

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: C07D 309/08, 211/54, 213/64, 401/06, 407/12, 413/12, 405/12, A61K 31/35, 31/445		A1	(11) International Publication Number: WO 98/39316 (43) International Publication Date: 11 September 1998 (11.09.98)
(21) International Application Number: PCT/US98/04297		Joseph, J. [US/US]; 1036 Johanna Drive, Ballwin, MO 63021 (US).	
(22) International Filing Date: 4 March 1998 (04.03.98)		(74) Agents: GAMSON, Edward, P. et al.; Welsh & Katz, Ltd., 22nd floor, 120 South Riverside Plaza, Chicago, IL 60606 (US).	
(30) Priority Data: Not furnished 4 March 1997 (04.03.97) US		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
<p>(71) Applicant (<i>for all designated States except US</i>): MONSANTO COMPANY [US/US]; 800 North Lindbergh Boulevard – 40E, St. Louis, MO 63167 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): BARTA, Thomas, E. [US/US]; Apartment #3W, 1133 Maple Avenue, Evanston, IL 60202 (US). BECKER, Daniel, P. [US/US]; 1427 Pebble Creek Drive, Glenview, IL 60025 (US). VILLAMIL, Clara, I. [US/US]; 813 Long Road, Glenview, IL 60025 (US). FRESKOS, John, N. [US/US]; 7572 York, Clayton, MO 63105 (US). MISCHKE, Brent, V. [US/US]; 25 White River Lane, Defiance, MO 63341 (US). MULLINS, Patrick, B. [US/US]; 7337 Raleigh, St. Louis, MO 63123 (US). HEINTZ, Robert, M. [US/US]; 603 Nancy Place, Ballwin, MO 63021 (US). GETMAN, Daniel, P. [US/US]; 66 Sunny Hill Court, Chesterfield, MO 63017 (US). McDONALD,</p>			

(54) Title: N-HYDROXY 4-SULFONYL BUTANAMIDE COMPOUNDS

(57) Abstract

An N-hydroxy sulfonyl butanamide compound that *inter alia* inhibits matrix metalloprotease activity is disclosed as is a treatment process that comprises administering a contemplated N-hydroxy sulfonyl butanamide compound in an MMP enzyme-inhibiting effective amount to a host having a condition associated with pathological matrix metall protease activity.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

N-HYDROXY 4-SULFONYL BUTANAMIDE COMPOUNDS

DescriptionTechnical Field

5 This invention is directed to proteinase (protease) inhibitors, and more particularly to N-hydroxy sulfonyl butanamide (hydroxamic acid) compounds that, inter alia, inhibit the activity of matrix metalloproteinases, compositions of those
10 inhibitors, intermediates for the syntheses of those compounds, processes for the preparation of the compounds and processes for treating pathological conditions associated with pathological matrix metalloproteinase activity.

15

Background of the Invention

Connective tissue, extracellular matrix constituents and basement membranes are required components of all mammals. These components are the
20 biological materials that provide rigidity, differentiation, attachments and, in some cases, elasticity to biological systems including human beings and other mammals. Connective tissues components include, for example, collagen, elastin,
25 proteoglycans, fibronectin and laminin. These biochemicals make up, or are components of structures, such as skin, bone, teeth, tendon, cartilage, basement membrane, blood vessels, cornea and vitreous humor.

30

Under normal conditions, connective tissue turnover and/or repair processes are controlled and in equilibrium. The loss of this balance for whatever reason is involved in a number of disease

-2-

states. Inhibition of the enzymes responsible for a loss of equilibrium provides a control mechanism for this tissue decomposition and, therefore, a treatment for these diseases.

5 Degradation of connective tissue or connective tissue components is carried out by the action of proteinase enzymes released from resident tissue cells and/or invading inflammatory or tumor cells. A major class of enzymes involved in this
10 function are the zinc metalloproteinases (metalloproteases, or MMPs).

The metalloprotease enzymes are divided into classes with some members having several different names in common use. Examples are:
15 collagenase I (MMP-1, fibroblast collagenase; EC 3.4.24.3), collagenase II (MMP-8, neutrophil collagenase; EC 3.4.24.34), collagenase III (MMP-13), stromelysin 1 (MMP-3; EC 3.4.24.17), stromelysin 2 (MMP-10; EC 3.4.24.22), proteoglycanase, matrilysin
20 (MMP-7), gelatinase A (MMP-2, 72kDa gelatinase, basement membrane collagenase; EC 3.4.24.24), gelatinase B (MMP-9, 92kDa gelatinase; EC 3.4.24.35), stromelysin 3 (MMP-11), metalloelastase (MMP-12, HME, human macrophage elastase) and membrane MMP (MMP-14).
25 MMP is an abbreviation or acronym representing the term Matrix Metalloprotease with the attached numerals providing differentiation between specific members of the MMP group.

The uncontrolled breakdown of connective
30 tissue by metalloproteases is a feature of many pathological conditions. Examples include rheumatoid arthritis, osteoarthritis, septic arthritis; corneal, epidermal or gastric ulceration; tumor metastasis,

-3-

invasion or angiogenesis; periodontal disease; proteinuria; Alzheimer's Disease; multiple sclerosis; coronary thrombosis and bone disease. Defective injury repair processes can also occur. This can 5 produce improper wound healing leading to weak repairs, adhesions and scarring. These latter defects can lead to disfigurement and/or permanent disabilities as with post-surgical adhesions.

Matrix metalloproteases are also involved 10 in the biosynthesis of tumor necrosis factor (TNF) and inhibition of the production or action of TNF and related compounds is an important clinical disease treatment mechanism. TNF- α , for example, is a cytokine that at present is thought to be produced 15 initially as a 28 kD cell-associated molecule. It is released as an active, 17 kD form that can mediate a large number of deleterious effects *in vitro* and *in vivo*. For example, TNF can cause and/or contribute to the effects of inflammation, rheumatoid arthritis, 20 autoimmune disease, multiple sclerosis, graft rejection, fibrotic disease, cancer, infectious diseases, malaria, mycobacterial infection, meningitis, fever, psoriasis, cardiovascular/pulmonary effects such as post- 25 ischemic reperfusion injury, congestive heart failure, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage and acute phase responses like those seen with infections and sepsis and during shock such as septic shock and hemodynamic shock.

30 Chronic release of active TNF can cause cachexia and anorexia. TNF can be lethal.

TNF- α convertase is a metalloproteinase involved in the formation of active TNF- α .

- 4 -

Inhibition of TNF- α convertase inhibits production of active TNF- α . Compounds that inhibit both MMPs activity have been disclosed in WIPO International Publication Nos. WO 94/24140, WO 94/02466 and WO 5 97/20824. There remains a need for effective MMP and TNF- α convertase inhibiting agents. Compounds that inhibit MMPs such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF (Gearing et al. *Nature* 376, 555-557 (1994), 10 McGeehan et al., *Nature* 376, 558-561 (1994)).

MMPs are involved in other biochemical processes in mammals as well. Included is the control of ovulation, post-partum uterine involution, possibly implantation, cleavage of APP (β -Amyloid Precursor Protein) to the amyloid plaque and inactivation of α_1 -protease inhibitor (α_1 -PI). Inhibition of these metalloproteases permits the control of fertility and the treatment or prevention of Alzheimers Disease. In addition, increasing and 20 maintaining the levels of an endogenous or administered serine protease inhibitor drug or biochemical such as α_1 -PI supports the treatment and prevention of diseases such as emphysema, pulmonary diseases, inflammatory diseases and diseases of aging 25 such as loss of skin or organ stretch and resiliency.

Inhibition of selected MMPs can also be desirable in other instances. Treatment of cancer and/or inhibition of metastasis and/or inhibition of angiogenesis are examples of approaches to the 30 treatment of diseases wherein the selective inhibition of stromelysin (MMP-3), gelatinase (MMP-2), gelatinase B (MMP-9) or collagenase III (MMP-13)

-5-

are the relatively most important enzyme or enzymes to inhibit especially when compared with collagenase I (MMP-1). A drug that does not inhibit collagenase I can have a superior therapeutic profile.

- 5 Osteoarthritis, another prevalent disease wherein it is believed that cartilage degradation in inflamed joints is at least partially caused by MMP-13 released from cells such as stimulated chondrocytes, may be best treated by administration of drugs one of
10 whose modes of action is inhibition of MMP-13. See, for example, Mitchell et al., *J. Clin. Invest.*, 97:761-768 (1996) and Reboul et al., *J. Clin. Invest.*, 97:2011-2019 (1996).

Inhibitors of metalloproteases are known.

- 15 Examples include natural biochemicals such as tissue inhibitor of metalloproteinase (TIMP), α_2 -macroglobulin and their analogs or derivatives. These are high molecular weight protein molecules that form inactive complexes with metalloproteases.
20 A number of smaller peptide-like compounds that inhibit metalloproteases have been described. Mercaptoamide peptidyl derivatives have shown ACE inhibition *in vitro* and *in vivo*. Angiotensin converting enzyme (ACE) aids in the production of
25 angiotensin II, a potent pressor substance in mammals and inhibition of this enzyme leads to the lowering of blood pressure.

- Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are
30 known as is shown in, for example, WO95/12389, WO96/11209 and U.S. 4,595,700. Hydroxamate group-containing MMP inhibitors are disclosed in a number of published patent applications such as WO 95/29892,

- 6 -

WO 97/24117, WO 97/49679 and EP 0 780 386 that disclose carbon back-boned compounds, and WO 90/05719, WO 93/20047, WO 95/09841 and WO 96/06074 that disclose hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones, as does the article by Schwartz et al., *Progr. Med. Chem.*, 29:271-334 (1992) and those of Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997) and Denis et al., *Invest. New Drugs*, 15(3): 175-185 (1997).

10 One possible problem associated with known MMP inhibitors is that such compounds often exhibit the same or similar inhibitory effects against each of the MMP enzymes. For example, the peptidomimetic hydroxamate known as batimastat is reported to
15 exhibit IC₅₀ values of about 1 to about 20 nanomolar (nM) against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat, another peptidomimetic hydroxamate was reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum very
20 similar to batimastat, except that marimastat exhibited an IC₅₀ value against MMP-3 of 230 nM.
Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997).

25 Meta analysis of data from Phase I/II studies using marimastat in patients with advanced, rapidly progressive, treatment-refractory solid tumor cancers (colorectal, pancreatic, ovarian, prostate) indicated a dose-related reduction in the rise of cancer-specific antigens used as surrogate markers
30 for biological activity. Although marimastat exhibited some measure of efficacy via these markers, toxic side effects were noted. The most common drug-related toxicity of marimastat in those clinical

- 7 -

trials was musculoskeletal pain and stiffness, often commencing in the small joints in the hands, spreading to the arms and shoulder. A short dosing holiday of 1-3 weeks followed by dosage reduction 5 permits treatment to continue. Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997). It is thought that the lack of specificity of inhibitory effect among the MMPs may be the cause of that effect.

In view of the importance of hydroxamate 10 MMP inhibitor compounds in the treatment of several diseases and the lack of enzyme specificity exhibited by two of the more potent drugs now in clinical trials, it would be a great benefit if hydroxamates of greater enzyme specificity could be found. This 15 would be particularly the case if the hydroxamate inhibitors exhibited strong inhibitory activity against one or more of MMP-2, MMP-9 or MMP-13 that are associated with several pathological conditions, while at the same time exhibiting limited inhibition 20 of MMP-1, an enzyme that is relatively ubiquitous and as yet not associated with any pathological condition. The disclosure that follows describes one family of hydroxamate MMP inhibitors that exhibit 25 those desirable activities

25

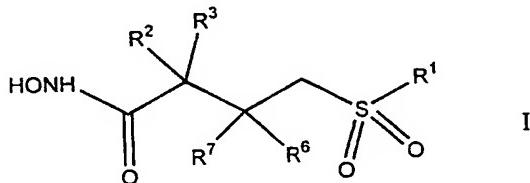
Brief Summary of the Invention

The present invention is directed to a family of molecules that among other properties inhibit matrix metalloprotease (MMP) activity, and 30 particularly inhibit the activity of one or more of MMP-2, MMP-9, or MMP-13, while generally exhibiting little activity against MMP-1. The present invention is also directed to processes for preparing a

-8-

contemplated compound and for treating a mammal having a condition associated with pathological matrix metalloprotease activity.

Briefly, one embodiment of the present invention is directed to a N-hydroxy sulfonyl butanamide (hydroxamic acid) compound that can act as a matrix metalloprotease enzyme inhibitor. That compound corresponds in structure to Formula I.



10

wherein

R¹ is a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted SO₂-group and having a length greater than about the length of a fully extended hexyl group and less than about the length of a fully extended eicosyl group, said R¹ defining a three-dimensional volume, when rotated about an axis drawn through the SO₂-bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the SO₂-bonded 1-position and the center of 3,4-bond of a 5-membered ring radical, whose widest dimension in a direction transverse to the axis of rotation is equivalent to about that of one furanyl ring to about that of two phenyl rings;

-9-

R² and R³ are independently selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, hydroxy-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy-C₁-C₄ hydrocarbyl, aryloxy-C₁-C₄ hydrocarbyl, amino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylthio-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylsulfonyl-C₁-C₄ hydrocarbyl, aminosulfonylamino-C₁-C₄ hydrocarbyl, aminocarbonylamino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylcarbonylamino-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl and benzyloxy-C₁-C₄ hydrocarbyl, but only one of R² and R³ is other than hydrido or C₁-C₄ hydrocarbyl; or

R² and R³ together with the depicted carbon atom to which they are bonded form a heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being substituted with a moiety R⁵ that is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen; and

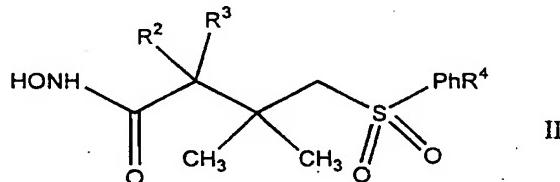
R⁶ and R⁷ are independently selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, hydroxy-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy-C₁-C₄ hydrocarbyl, aryloxy-C₁-C₄ hydrocarbyl, amino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylthio-C₁-C₄ hydrocarbyl,

-10-

C₁-C₄ hydrocarbylsulfonyl-C₁-C₄ hydrocarbyl,
aminosulfonylamino-C₁-C₄ hydrocarbyl,
aminocarbonylamino-C₁-C₄ hydrocarbyl, C₁-C₄
hydrocarbylcarbonylamino-C₁-C₄ hydrocarbyl, aryl-C₁-
5 C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl and
benzyloxy-C₁-C₄ hydrocarbyl, but only one of R⁶ and
R⁷ is other than hydrido or C₁-C₄ hydrocarbyl; or
R⁶ and R⁷ together with the depicted carbon
atom to which they are bonded form a heterocyclic
10 ring in which the heteroatom is oxygen, sulfur or
nitrogen, said heteroatom being optionally
substituted with one or two oxygens when sulfur and
being substituted with a moiety R⁵ that is selected
from the group consisting of a hydrido, C₁-C₄
15 hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄
carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl
group when nitrogen;
only one of R², R³, R⁶ and R⁷ is other than
hydrido, C₁-C₄ hydrocarbyl or forms part of a
20 heterocyclic ring structure as recited.
In preferred embodiments, R² is selected
from the group consisting of a hydrido, C₁-C₄
hydrocarbyl, N-piperidinyl, N-piperazinyl, N-(C₁-C₄
hydrocarbyl)piperazinyl, N-pyrrolidinyl, N-
25 morpholinyl and -Y-Z group, wherein -Y is -O or -
NR¹¹, wherein R¹¹ is hydrido or C₁-C₄ hydrocarbyl,
and -Z is selected from the group consisting of a
hydrido, C₁-C₄ hydrocarbyl, benzoyl, (2-
30 pyridinyl)methyl, (3-pyridinyl)methyl or (4-
pyridinyl)methyl, 2-(morpholinyl)ethyl, 2-

-11-

(piperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(N-methylpiperazinyl)ethyl, 2-(thiomorpholinyl)ethyl, 2-(thiomorpholinyl sulfone)ethyl, 2-(succinimidyl)ethyl, 2-(hydantoinyl), 2-(3-methylhydantoinyl)ethyl, 2-(N-C₁-C₄ hydrocarbylamino)ethyl, 2-[N,N-di(C₁-C₄ hydrocarbyl)amino]ethyl, carboxy C₁-C₄ hydrocarbyl, piperidinyl, 2-, 3-, or 4-pyridinyl, sulfonamido, C₁-C₄ hydrocarbylsulfonyl, C₁-C₄ hydrocarbylphosphonyl
 10 and C(O)-W wherein -W is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy -CHR¹²NH₂ wherein R¹² is the side chain of a D or L amino acid, benzyloxy, benzylamino and amino group, or R² and R³ together form a
 15 heterocyclic ring, and R⁶ and R⁷ are both either hydrido or methyl. In one of those embodiments, a contemplated compound corresponds in structure
 Formula II:



20

wherein

Ph is a phenyl radical bonded directly to the depicted SO₂-group that is itself substituted at its
 25 own 4-position with a substituent R⁴ selected from the group consisting of one other single-ringed aryl or heteroaryl group, a C₃-C₁₄ hydrocarbyl group, a

-12-

C₂-C₁₄ hydrocarbyloxy group, a phenoxy group, a thiophenoxy group, a 4-thiopyridyl group, a phenylazo group, a phenylureido group, a nicotinamido group, an isonicotinamido group, a picolinamido group, an 5 anilino group and a benzamido group;

R² is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, N-piperidinyl, N-piperazinyl, N-(C₁-C₄ hydrocarbyl)piperazinyl, N-pyrrolidinyl, N-morpholinyl and -Y-Z group, wherein - 10 Y is -O or -NR¹¹, wherein R¹¹ is hydrido or C₁-C₄ hydrocarbyl, and -Z is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, benzoyl, (2-pyridinyl)methyl, (3-pyridinyl)methyl or (4-pyridinyl)methyl, 2-(morpholinyl)ethyl, 2- 15 (piperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(N-methylpiperazinyl)ethyl, 2-(thiomorpholinyl)ethyl, 2-(thiomorpholinyl sulfone)ethyl, 2-(succinimidyl)ethyl, 2-(hydantoinyl), 2-(3-methylhydantoinyl)ethyl, 2-(N-C₁-C₄ 20 hydrocarbylamino)ethyl, 2-[N,N-di(C₁-C₄ hydrocarbyl)amino]ethyl, carboxy C₁-C₄ hydrocarbyl, piperidinyl, 2-, 3-, or 4-pyridinyl, sulfonamido, C₁-C₄ hydrocarbylsulfonyl, C₁-C₄ hydrocarbylphosphonyl and C(O)-W wherein -W is selected from the group 25 consisting of a hydrido, C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy -CHR¹²NH₂ wherein R¹² is the side chain of a D or L amino acid, benzyloxy, benzylamino and amino group;

R³ is a hydrido or C₁-C₄ hydrocarbyl group; or

-13-

R² and R³ together with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being substituted with a moiety R⁵ that is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen.

A process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity is also contemplated. That process comprises administering a compound described hereinbefore in an enzyme-inhibiting effective amount to a mammalian host having such a condition. The use of repeated administrations is particularly contemplated.

Among the several benefits and advantages of the present invention are the provision of compounds and compositions effective as inhibitors of matrix metalloproteinase activity, and the provision of such compounds and compositions that are effective for the inhibition of metalloproteinases implicated in diseases and disorders involving uncontrolled breakdown of connective tissue.

More particularly, a benefit of this invention is the provision of a compound and composition effective for inhibiting metalloproteinases, particularly MMP-13 and/or MMP-2, associated with pathological conditions such as, for example, rheumatoid arthritis, osteoarthritis, septic

-14-

arthritis, corneal, epidermal or gastric ulceration, tumor metastasis, invasion or angiogenesis, periodontal disease, proteinuria, Alzheimer's Disease, coronary thrombosis, multiple sclerosis and
5 bone disease.

An advantage of the invention is the provision of a method for preparing such compositions. Another benefit is the provision of a method for treating a pathological condition
10 associated with abnormal matrix metalloproteinase activity.

Another advantage of the invention is the provision of compounds, compositions and methods effective for treating such pathological conditions
15 by selective inhibition of a metalloproteinase such as MMP-13 and MMP-2 associated with such conditions with minimal side effects resulting from inhibition of other proteinases such as MMP-1, whose activity is necessary or desirable for normal body function.

20 Still further benefits and advantages of the invention will be apparent to the skilled worker from the disclosure that follows.

Detailed Description of Preferred Embodiments

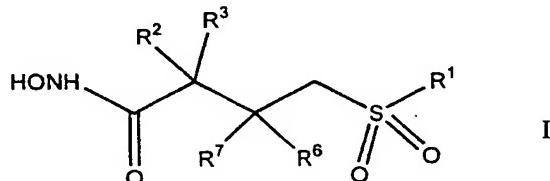
25 In accordance with the present invention, it has been found that certain N-hydroxy sulfonyl butanamide (hydroxamic acid) compounds, also referred to herein as sulfonyl butanhydroxamate compounds, are effective, *inter alia*, for inhibition of matrix
30 metalloproteinases ("MMPs") believed to be associated with uncontrolled or otherwise pathological breakdown of connective tissue. In particular, it has been found that these certain sulfonyl butanhydroxamate

-15-

compounds are effective for inhibition of collagenase III (MMP-13) and also gelatinase A (MMP-2), which can be particularly destructive to tissue if present or generated in abnormal quantities or concentrations,
5 and thus exhibit a pathological activity.

Moreover, it has been discovered that many of these sulfonyl butanhydroxamate compounds are selective in the inhibition of MMPs associated with diseased conditions without excessive inhibition of
10 other collagenases essential to normal bodily function such as tissue turnover and repair. More particularly, it has been found that particularly preferred the sulfonyl butanhydroxamate compounds are particularly active in inhibiting of MMP-13 and/or
15 MMP-2, while having a limited or minimal effect on MMP-1. This point is discussed in detail hereinafter and is illustrated in the Inhibition Table hereinafter.

One embodiment of the present invention is
20 directed to a sulfonyl butanhydroxamate compound that can act as a matrix metalloprotease enzyme inhibitor. That compound corresponds in structure to Formula I



25

wherein

R¹ is a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or
30 heteroaryl radical bonded directly to the depicted

-16-

SO₂-group and having a length that is equivalent to a length that is greater than about that of a fully extended hexyl group and less than about that of a fully extended eicosyl group. In addition, R¹ defines
5 a three-dimensional volume, when rotated about an axis drawn through the SO₂-bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the SO₂-bonded 1-position and the center of 10 3,4-bond of a 5-membered ring radical, whose widest dimension in a direction transverse to the axis of rotation is equivalent to about that of one furanyl ring to about that of two phenyl rings;

R² and R³ are independently selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl,
15 heteroaryl-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, hydroxy-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy-C₁-C₄ hydrocarbyl, aryloxy-C₁-C₄ hydrocarbyl, amino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylthio-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylsulfonyl-C₁-C₄ hydrocarbyl,
20 aminosulfonylamino-C₁-C₄ hydrocarbyl, aminocarbonylamino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylcarbonylamino-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl and
benzyloxy-C₁-C₄ hydrocarbyl, but only one of R² and
25 R³ is other than hydrido or C₁-C₄ hydrocarbyl; or

R² and R³ together with the depicted carbon atom to which they are bonded form a heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally
30 substituted with one or two oxygens when sulfur and

-17-

being substituted with a moiety R⁵ that is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl
5 group when nitrogen; and

R⁶ and R⁷ are independently selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, hydroxy-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy-C₁-C₄
10 hydrocarbyl, aryloxy-C₁-C₄ hydrocarbyl, amino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylthio-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylsulfonyl-C₁-C₄ hydrocarbyl, aminosulfonylamino-C₁-C₄ hydrocarbyl, aminocarbonylamino-C₁-C₄ hydrocarbyl, C₁-C₄
15 hydrocarbylcarbonylamino-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl and benzyloxy-C₁-C₄ hydrocarbyl, but only one of R⁶ and R⁷ is other than hydrido or C₁-C₄ hydrocarbyl; or

R⁶ and R⁷ together with the depicted carbon atom to which they are bonded form a heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being substituted with a moiety R⁵ that is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl
25 group when nitrogen;

-18-

only one of R², R³, R⁶ and R⁷ is other than hydrido, C₁-C₄ hydrocarbyl or forms part of a heterocyclic ring structure as recited.

As noted above, an R¹ substituent contains
5 a 5- or 6-membered cyclohydrocarbyl, heterocyclo,
aryl or heteroaryl radical bonded directly to the
depicted SO₂-group. An R¹ substituent also has
length, width and substitution requirements that are
discussed in detail below. It is noted here,
10 however, that a single- ringed or fused ring
cyclohydrocarbyl, heterocyclo, aryl or heteroaryl
radical is not itself long enough to fulfill the
length requirement. As such, that cyclohydrocarbyl,
heterocyclo, aryl or heteroaryl radical must itself
15 be substituted.

Exemplary 5- or 6-membered
cyclohydrocarbyl, heterocyclo, aryl or heteroaryl
radicals that can constitute a portion of a R¹
substituent and are themselves substituted as
20 discussed herein include phenyl, 2-, 3-, or 4-
pyridyl, 2-naphthyl, 2-pyrazinyl, 2- or 5-
pyrimidinyl, 2- or 3-benzo(b)thienyl, 8-purinyl, 2-
or 3-furyl, 2- or 3-pyrrolyl, 2-imidazolyl,
25 cyclopentyl, cyclohexyl, 2- or 3-piperidinyl, 2- or
3-morpholinyl, 2- or 3-tetrahydropyranyl, 2-
imidazolidinyl, 2- or 3-pyrazolidinyl and the like.
A phenyl radical is particularly preferred and is
used illustratively herein.

When examined along its longest chain of
30 atoms, an R¹ substituent, including its own
substituent when present, has a total length
equivalent to a length that is greater than that of a

-19-

fully extended saturated chain of six carbon atoms (a hexyl group); i.e., a length of a fully extended heptyl chain or longer, and a length that is less than that of a fully extended saturated chain of 5 about 20 carbons (an eicosyl group). Preferably, that length is equivalent to a length of a fully extended saturated chain of about 8 to about 18 carbon atoms, even though many more atoms may be present in ring structures or substituents. This 10 length requirement is discussed further below.

Looked at more generally, and aside from specific moieties from which it is constructed, an R¹ substituent (radical, group or moiety) has a length equivalent to that of a fully extended heptyl group 15 or greater. Such an R¹ substituent also has a length that is less than that of a fully extended eicosyl group. That is to say that a R¹ is a substituent having a length greater than that of a saturated six carbon chain and shorter than that of a saturated 20 twenty carbon chain, and more preferably, a length greater than that of a octyl group and less than that of a palmityl group. The radical chain lengths are measured along the longest linear atom chain in the radical, following the skeletal atoms of a ring where 25 necessary. Each atom in the chain, e.g. carbon, oxygen or nitrogen, is presumed to be carbon for ease in calculation.

Such lengths can be readily determined by using published bond angles, bond lengths and atomic 30 radii, as needed, to draw and measure a chain, or by building models using commercially available kits whose bond angles, lengths and atomic radii are in accord with accepted, published values. Radical

-20-

(substituent) lengths can also be determined somewhat less exactly by presuming, as is done here, that all atoms have bond lengths of saturated carbon, that unsaturated and aromatic bonds have the same lengths
5 as saturated bonds and that bond angles for unsaturated bonds are the same as those for saturated bonds, although the above-mentioned modes of measurement are preferred. For example, a 4-phenyl or 4-pyridyl group has a length of a four carbon
10 chain, as does a propoxy group, whereas a biphenyl group has a length of about an eight carbon chain using a contemplated measurement mode.

In addition, an R¹ substituent, when rotated about an axis drawn through the SO₂-bonded
15 1-position and the 4-position of a 6-membered ring radical or the SO₂-bonded 1-position and through the 3,4 bond of a 5-membered ring radical defines a three-dimensional volume whose widest dimension has the width equivalent to that of about one furanyl
20 ring to about the width of two phenyl rings in a direction transverse to that axis to rotation.

When utilizing this width or volume criterion, a fused ring system such as a naphthyl or purinyl radical is considered to be a 6- or 5-membered ring that is substituted at appropriate positions numbered from the SO₂-linkage that is deemed to be at the 1-position as discussed before. Thus, a 2-naphthyl substituent or an 8-purinyl substituent is an appropriately sized R¹ radical as to width when examined using the above rotational width criterion. On the other hand, a 1-naphthyl group or a 7- or 9-purinyl group is too large upon rotation and is excluded.

-21-

As a consequence of these length and width requirements, R¹ substituents such as 4-(phenyl)phenyl [biphenyl], 4-(4'-methoxyphenyl)phenyl, 4-(phenoxy)phenyl, 5 4-(thiophenyl)phenyl [4-(phenylthio)phenyl], 4-(phenylazo)phenyl 4-(phenylureido)phenyl, 4-(anilino)phenyl, 4-(nicotinamido)phenyl, 4-(isonicotinamido)phenyl, 4-(picolinamido)phenyl and 4-(benzamido)phenyl are among particularly preferred 10 R¹ substituents, with 4-(phenoxy)phenyl and 4-(thiophenyl)phenyl being most preferred.

An SO₂-linked cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is a 5- or 6-membered single-ring that is itself substituted 15 with one other substituent, R⁴. The SO₂-linked single-ringed cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is R⁴-substituted at its own 4-position when a 6-membered ring and at its own 3-position when a 5-membered ring. The 20 cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical to which R⁴ is bonded is preferably a phenyl group, so that R¹ is preferably PhR⁴ in which R⁴ is bonded at the 4-position of the SO₂-linked phenyl (Ph) radical, and in which R⁴ can itself be 25 optionally substituted as is discussed hereinafter. Substitution at the 2-position of a SO₂-linked cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical appears to greatly lessen inhibitory potency toward MMP enzymes, and is absent from a contemplated 30 compound.

A contemplated R⁴ substituent can be a single-ringed cyclohydrocarbyl, heterocyclo, aryl or

-22-

heteroaryl group or another substituent having a chain length of 3 to about 14 carbon atoms such as a hydrocarbyl or hydrocarbyloxy group [e.g., C₃-C₁₄ hydrocarbyl or O-C₂-C₁₄ hydrocarbyl], a phenyl group,
5 a phenoxy group [-OC₆H₅], a thiophenoxy group [phenylsulfanyl; -SC₆H₅], an anilino group [-NHC₆H₅], a phenylazo group [-N₂C₆H₅], a phenylureido group [aniline carbonylamino; -NHC(O)NH-C₆H₅], a benzamido group [-NHC(O)C₆H₅], a nicotinamido group
10 [3-NHC(O)C₅H₄N], an isonicotinamido group [4-NHC(O)C₅H₄N], or a picolinamido group [2-NHC(O)C₅H₄N]. As noted before in conjunction with the discussion of R¹, most preferred R⁴ substituents are phenoxy and thiophenoxy groups that are
15 preferably themselves free of substitution.
Additionally contemplated R⁴ substituent groups include a heterocyclo, heterocyclohydrocarbyl, arylhydrocarbyl, arylheterocyclohydrocarbyl, heteroarylhydrocarbyl,
20 heteroarylheterocyclohydrocarbyl, arylhydrocarbyloxyhydrocarbyl, aryloxyhydrocarbyl, hydrocarboylhydrocarbyl, arylhydrocarboylhydrocarbyl, arylcarbonylhydrocarbyl, arylazoaryl, arylhydrazinoaryl, hydrocarbylthiohydrocarbyl,
25 hydrocarbylthioaryl, arylthiohydrocarbyl, heteroarylthiohydrocarbyl, hydrocarbylthioarylhydrocarbyl, arylhydrocarbylthiohydrocarbyl, arylhydrocarbylthioaryl, arylhydrocarbylamino,
30 heteroarylhydrocarbylamino, and a heteroarylthio group.

-23-

A contemplated R⁴ substituent can itself also be substituted with one or more substituent radicals at the meta- or para-position or both of a six-membered ring with a single atom or a substituent containing a longest chain of up to ten atoms, excluding hydrogen. Exemplary substituent radicals include a halo, hydrocarbyl, hydrocarbyloxy, nitro, cyano, perfluorohydrocarbyl, trifluoromethylhydrocarbyl, hydroxy, mercapto, hydroxycarbonyl, aryloxy, arylthio, arylamino, arylhydrocarbyl, aryl, heteroaryloxy, heteroarylthio, heteroarylamino, heteroarylhydrocarbyl, hydrocarbyloxycarbonylhydrocarbyl, heterocyclooxy, hydroxycarbonylhydrocarbyl, heterocyclothio, heterocycloamino, cyclohydrocarbyloxy, cyclohydrocarbylthio, cyclohydrocarbylamino, heteroarylhydrocarbyloxy, heteroarylhydrocarbylthio, heteroarylhydrocarbylamino, arylhydrocarbyloxy, arylhydrocarbylthio, arylhydrocarbylamino, heterocyclic, heteroaryl, hydroxycarbonylhydrocarbyloxy, alkoxycarbonylalkoxy, hydrocarbyloyl, arylcarbonyl, arylhydrocarbyloyl, hydrocarboxyloxy, arylhydrocarboyoxy, hydroxyhydrocarbyl, hydroxyhydrocarbyloxy, hydrocarbylthio, hydrocarbyloxyhydrocarbylthio, hydrocarbyloxy, hydroxycarbonylhydrocarbyloxy, hydrocarbyloxyhydrocarbyl, hydrocarbylhydroxycarbonylhydrocarbylthio, hydrocarbyloxyhydrocarbylhydrocarbyloxy, hydrocarbyloxyhydrocarbylthio, amino, hydrocarbylcarbonylamino, arylcarbonylamino, cyclohydrocarbylcarbonylamino,

- 24 -

heterocyclohydrocarbylcarbonylamino,
arylhydrocarbylcarbonylamino,
heteroarylcarbonylamino,
heteroarylhydrocarbylcarbonylamino,
5 heterocyclohydrocarbyloxy, hydrocarbysulfonylamino,
arylsulfonylamino, arylhydrocarbysulfonylamino,
heteroarylsulfonylamino, heteroarylhydrocarbyl-
sulfonylamino, cyclohydrocarbysulfonylamino,
heterocyclohydrocarbysulfonylamino and N-
10 monosubstituted or N,N-disubstituted aminohydrocarbyl
group wherein the substituent(s) on the nitrogen are
selected from the group consisting of hydrocarbyl,
aryl, arylhydrocarbyl, cyclohydrocarbyl,
arylhydrocarbyloxycarbonyl, hydrocarbyloxycarbonyl,
15 and hydrocarboyl, or wherein the nitrogen and two
substituents attached thereto form a 5- to 8-membered
heterocyclic or heteroaryl ring group.

Thus, initial studies indicate that so long
as the length, substitution and width (volume upon
20 rotation) requirements of an SO₂-linked R¹
substituent discussed herein are met, an R¹
substituent can be extremely varied.

A particularly preferred R⁴ substituent of
an SO₂-linked Ph group is a single-ringed aryl or
25 heteroaryl, phenoxy, thiophenoxy, phenylazo,
phenylureido, nicotinamido, isonicotinamido,
picolinamido, anilino or benzamido group that is
unsubstituted or is itself substituted (optionally
substituted) at the para-position when a 6-membered
30 ring or the 3-position when a 5-membered ring. Here,
single atoms such as halogen moieties or substituents
that contain one to a chain of about ten atoms other

-25-

than hydrogen such as C₁-C₁₀ hydrocarbyl, C₁-C₉ hydrocarbyloxy or carboxyethyl groups can be used.

Exemplary particularly preferred substituted PhR⁴ (particularly preferred substituted R¹) substituents include biphenyl, 4-phenoxyphenyl, 4-thiophenoxyphenyl, 4-benzamidophenyl, 4-phenylureido, 4-anilinophenyl, 4-nicotinamido, 4-isonicotinamido, and 4-picolinamido. Exemplary particularly preferred R⁴ groups contain a 6-membered aromatic ring and include a phenyl group, a phenoxy group, a thiophenoxy group, a phenylazo group, a phenylureido group, an anilino group, a nicotinamido group, an isonicotinamido group, a picolinamido group and a benzamido group.

More specifically, a particularly preferred sulfonyl butanhydroxamate compounds has an R⁴ substituent that is a phenyl group, a phenoxy group, a thiophenoxy group, a phenylazo group, a phenylureido group, an anilino group, a nicotinamido group, an isonicotinamido group, a picolinamido group or a benzamido group that is itself optionally substituted at its own meta or para-position or both with a moiety that is selected from the group consisting of a halogen, a C₁-C₉ hydrocarbyloxy (-O-C₁-C₉ hydrocarbyl) group, a C₁-C₁₀ hydrocarbyl group, a di-C₁-C₉ hydrocarbylamino [-N(C₁-C₉ hydrocarbyl)(C₁-C₉ hydrocarbyl)] group, a carboxyl C₁-C₈ hydrocarbyl (C₁-C₈ hydrocarbyl-CO₂H) group, a C₁-C₄ hydrocarbyloxy carbonyl C₁-C₄ hydrocarbyl [C₁-C₄ hydrocarbyl-O-(CO)-C₁-C₄ hydrocarbyl] group, a C₁-C₄ hydrocarbyloxycarbonyl C₁-C₄ hydrocarbyl [C₁-C₄

-26-

hydrocarbyl (CO)-O-C₁-C₄ hydrocarbyl] group and a C₁-C₈ hydrocarbyl carboxamido [-NH(CO)-C₁-C₈ hydrocarbyl] group, or is substituted at the meta- and para-positions by two methyl groups or by a C₁-C₂ alkylatedioxy group such as a methylenedioxy group.

Inasmuch as a contemplated SO₂-linked cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is itself preferably substituted with a 6-membered aromatic ring, two nomenclature systems are used together herein for ease in understanding substituent positions. The first system uses position numbers for the ring directly bonded to the SO₂-group, whereas the second system uses ortho, meta or para for the position of one or more substituents of a 6-membered ring bonded to a SO₂-linked cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical. When a R⁴ substituent is other than a 6-membered ring, substituent positions are numbered from the position of linkage to the aromatic or heteroaromatic ring. Formal chemical nomenclature is used in naming particular compounds.

Thus, the 1-position of an above-discussed SO₂-linked cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is the position at which the SO₂-group is bonded to the ring. The 4- and 3-positions of rings discussed here are numbered from the sites of substituent bonding from the SO₂-linkage as compared to formalized ring numbering positions used in heteroaryl nomenclature.

R² and R³ are independently selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl,

-27-

heteroaryl-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl,
hydroxy-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy-C₁-C₄
hydrocarbyl, aryloxy-C₁-C₄ hydrocarbyl, amino-C₁-C₄
hydrocarbyl, C₁-C₄ hydrocarbylthio-C₁-C₄ hydrocarbyl,
5 C₁-C₄ hydrocarbysulfonyl-C₁-C₄ hydrocarbyl,
aminosulfonylamino-C₁-C₄ hydrocarbyl,
aminocarbonylamino-C₁-C₄ hydrocarbyl, C₁-C₄
hydrocarbylcarbonylamino-C₁-C₄ hydrocarbyl, aryl-C₁-
C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl and
10 benzyloxy-C₁-C₄ hydrocarbyl. However, only one of R²
and R³ is other than hydrido or C₁-C₄ hydrocarbyl,
with hydrido being the preferred substituent.

Alternatively, R² and R³ together with the
depicted carbon atom to which they are bonded form a
15 heterocyclic ring, preferably a six-membered ring, in
which the heteroatom is oxygen, sulfur or nitrogen.
That heteroatom is optionally substituted with one or
two oxygens when sulfur and is substituted with a
moiety R⁵ that is selected from the group consisting
20 of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆
cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and
sulfonyl C₁-C₄ hydrocarbyl group when nitrogen.

R⁶ and R⁷ are independently selected from
the group consisting of a hydrido, C₁-C₄ hydrocarbyl,
25 heteroaryl-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl,
hydroxy-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy-C₁-C₄
hydrocarbyl, aryloxy-C₁-C₄ hydrocarbyl, amino-C₁-C₄
hydrocarbyl, C₁-C₄ hydrocarbylthio-C₁-C₄ hydrocarbyl,
C₁-C₄ hydrocarbysulfonyl-C₁-C₄ hydrocarbyl,

-28-

aminosulfonylamino-C₁-C₄ hydrocarbyl,
aminocarbonylamino- C₁-C₄ hydrocarbyl, C₁-C₄
hydrocarbylcarbonylamino-C₁-C₄ hydrocarbyl, aryl-C₁-
C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl and
5 benzyloxy-C₁-C₄ hydrocarbyl. Again, only one of R⁶
and R⁷ is other than hydrido or C₁-C₄ hydrocarbyl,
with both substituents preferably being either
hydrido or methyl.

Alternatively, R⁶ and R⁷ together with the
10 depicted carbon atom to which they are bonded form a
heterocyclic ring in which the heteroatom is oxygen,
sulfur or nitrogen. That heteroatom is optionally
substituted with one or two oxygens when sulfur and
is substituted with a moiety R⁵ that is selected from
15 the group consisting of a hydrido, C₁-C₄ hydrocarbyl,
C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl,
and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen.

Preferred R⁶ and R⁷ substituents and
heterocyclic rings are the same as those noted above
20 for R² and R³, and therefore will not be repeated
here.

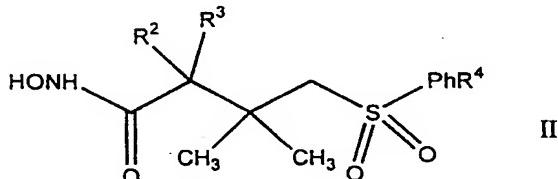
It is to be noted that only one of R², R³,
R⁶ and R⁷ is other than hydrido, C₁-C₄ hydrocarbyl or
forms part of a heterocyclic ring structure as
25 recited. Thus, the presence of two substituents on
two adjacent carbon atoms other than hydrido or C₁-C₄
hydrocarbyl is not contemplated, nor is the presence
of two heterocyclic rings on adjacent carbons.

In preferred embodiments, R⁶ and R⁷ are
30 preferably both either hydrido or methyl.

-29-

In one particularly preferred embodiment, a contemplated compound corresponds in structure to Formula II, wherein preferred R² and R³ substituents are as defined below, and R¹ is PhR⁴ wherein Ph is phenyl substituted at the 4-position with substituent R⁴ that is defined hereinabove. It is noted that preferred R² and R³ substituents need not be present only when R¹ is PhR⁴, and can be present with any R¹ substituent.

10



In preferred embodiments, an R² substituent is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, N-piperidinyl, N-piperazinyl, N-(C₁-C₄ hydrocarbyl)piperazinyl, N-pyrrolidinyl, N-morpholinyl and a -Y-Z group, wherein -Y is -O or -NR¹¹, R¹¹ is hydrido or C₁-C₄ hydrocarbyl, and -Z is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, benzoyl, (2-pyridinyl)methyl, (3-pyridinyl)methyl or (4-pyridinyl)methyl, 2-(morpholinyl)ethyl, 2-(piperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(N-methylpiperazinyl)ethyl, 2-(thiomorpholinyl)ethyl, 2-(thiomorpholinyl sulfone)ethyl, 2-(succinimidyl)ethyl, 2-(hydantoinyl), 2-(3-methylhydantoinyl)ethyl, 2-(N-C₁-C₄ hydrocarbylamino)ethyl, 2-[N,N-di(C₁-C₄

-30-

hydrocarbyl)amino]ethyl, carboxy C₁-C₄ hydrocarbyl, piperidinyl, 2-, 3-, or 4-pyridinyl, sulfonamido, C₁-C₄ hydrocarbysulfonyl, C₁-C₄ hydrocarbylphosphonyl and C(O)-W wherein -W is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy -CHR¹²NH₂ wherein R¹² is the side chain of a D or L amino acid, benzyl oxy, benzylamino and amino group. Thus, where -Y is -O and -Z is hydrido, R² (-Y-Z) is hydroxyl. Similarly, where -Y is NH and -Z is hydrido, R² is amino (-NH₂).

Exemplary amino acid side chains are those of the naturally occurring L amino acids that can be present in D or L configuration or a mixture thereof. The side chains of the so-called modified and unusual amino acids listed in 37 C.F.R § 1.822 are also contemplated here, and those side chains can be present in a D or L configuration or as a mixture.

Preferably, R³ is a hydrido or C₁-C₄ hydrocarbyl group. More preferably, R³ is hydrido.

Alternatively, R² and R³ together with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen. That heteroatom can be optionally substituted with one or two oxygens when sulfur and can be optionally substituted with a moiety, R⁵, selected from the group consisting of a C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl such as cyclopropyl, cyclobutyl, cyclopentenyl and cyclohexenyl, C₁-C₄ carbonylhydrocarbyl such as formyl, acetyl, acryloyl, and butyryl, and sulfonyl

-31-

C_1-C_4 hydrocarbyl group such as methylsulfonyl, ethylsulfonyl and the like when nitrogen. Thus, R^2 and R^3 together with their jointly-bonded carbon atom can form a 4-tetrahydrothiopyranyl group, its 5 corresponding sulfoxide or sulfone, a 4-piperidinyl or a 4-tetrahydropyranyl group. When present, the 4-piperidinyl group can be N-substituted with an above-described R^5 substituent.

When R^3 is hydrido, as is more preferred, 10 particularly preferred R^2 groups include amino, hydroxyl, 2-, 3- and 4-pyridylmethyl, N-pyrrolidinylmethyl and N-piperidinyl. Where R^2 and R^3 together with their jointly-bonded carbon atom form a six-membered heterocyclic ring, that 15 heteroatom is preferably nitrogen that is optionally substituted as discussed before.

The length of an R^1 substituent bonded to the SO_2 group is believed to play a role in the overall activity of a contemplated inhibitor compound 20 against MMP enzymes generally. Thus, a compound having an R^1 substituent that is shorter in length than a heptyl group, e.g., a 4-methoxyphenyl group (compound of Example 6), typically exhibits moderate to poor inhibitory activity against all of the MMP 25 enzymes, whereas compounds whose R^1 substituents have a length of about an heptyl chain or longer, e.g., a 4-phenoxyphenyl group (compound of Example 5) that has a length of about a nine-carbon chain, typically exhibit good to excellent potencies against MMP-13 or 30 MMP-2 and also selectivity against MMP-1. Exemplary data are provided in the Inhibition Table hereinafter

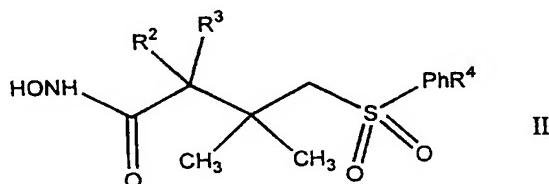
-32-

in which the activities of the above two compounds can be compared.

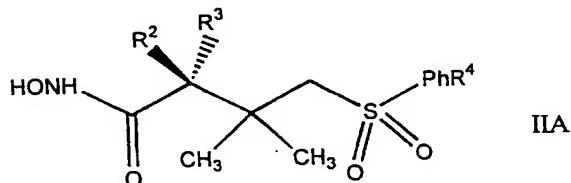
The data of that Table also illustrate that compounds having an R³ group that is hydrido and a nitrogen-containing R² substituent are particularly effective inhibitors of the activity of MMP-2, while maintaining minimal activity against MMP-1.

In view of the above-discussed preferences, compounds corresponding in structure to particular formulas constitute particularly preferred 10 embodiments.

In one of those embodiments, a contemplated compound corresponds in structure to Formula II, below, wherein preferred R², R³ substituents and PhR⁴ 15 are as defined above.



A compound of Formula II is preferably present in the stereoconfiguration of Formula IIIA, 20 below



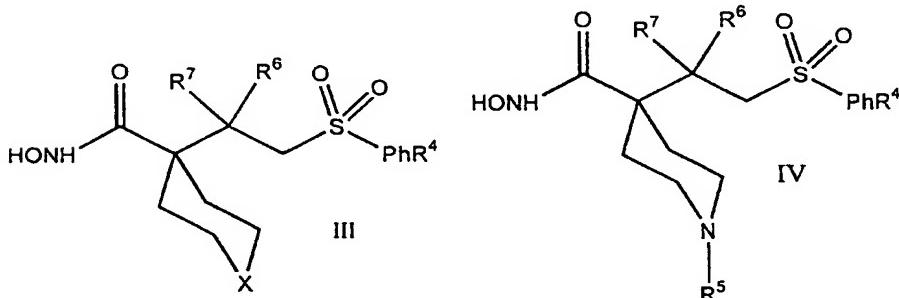
In yet another group of preferred compounds, R² and R³ together with the carbon atom to

-33-

which they are bonded form a six-membered heterocyclic ring whose heteroatom, X, is O, S, S(O), S(O₂) or NR⁵, e.g., a 4-piperidinyl, tetrahydropyranyl or tetrahydrothiopyranyl group.

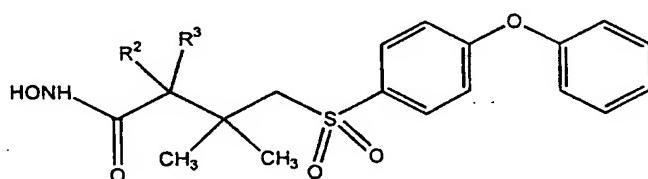
- 5 The nitrogen of the 4-piperidinyl group is substituted with a moiety R⁵ selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and a sulfonyl C₁-C₄ hydrocarbyl group. The R⁶ and R⁷
- 10 substituents here are both a hydrido or C₁-C₄ hydrocarbyl group, preferably methyl. Those preferred compounds correspond in structure generally and specifically to Formulas III and IV, respectively

15



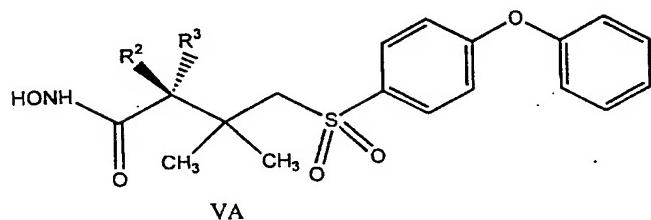
Following the preference that each of R⁶ and R⁷ be methyl, and the preference that R¹ be PhR⁴,

- 20 which in turn is phenoxypyhenyl or 4-thiophenoxyphenyl, another particularly preferred compound corresponds in structure to Formula V, below

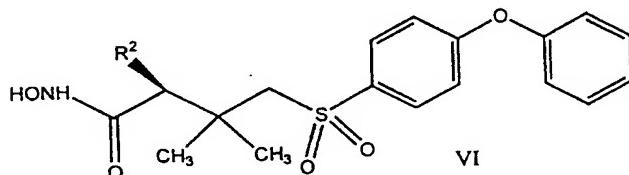


-34-

The preferred stereoconfiguration of a compound of Formula V is illustrated in Formula VA,
5 below

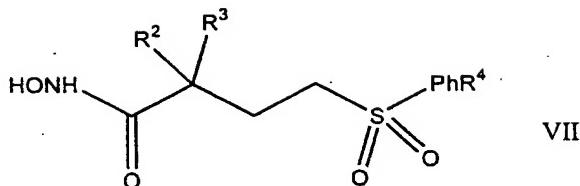


Taking in to consideration the further preference that R³ be a hydrido group, a presently
10 most preferred compound corresponds in
stereoconfiguration to Formula VI, below

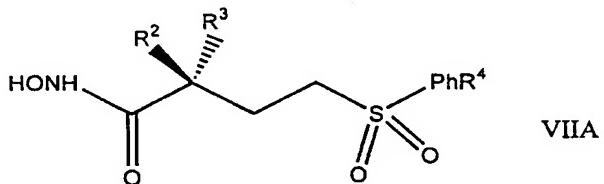


15 In another of those embodiments in which the preference for R⁶ and R⁷ both being hydrido, a contemplated compound corresponds in structure to
the 20 contemplated compound corresponds in structure to
Formula VII, below, wherein R², R³ and PhR⁴ are as defined above.

-35-

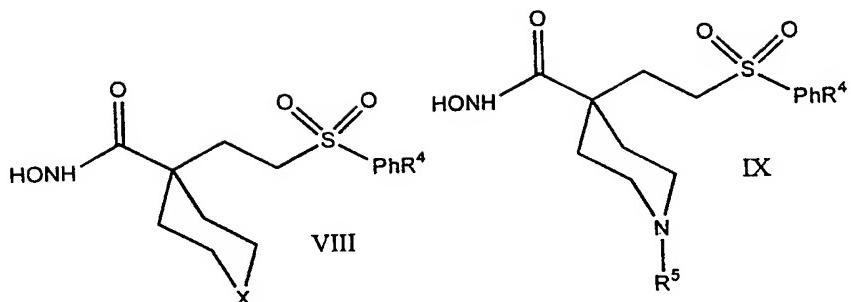


A above compound of this embodiment
 preferably has the stereoconfiguration shown in
 5 Formula VIIA, below



In a further group of preferred compounds
 of this embodiment, R² and R³ together with the
 carbon atom to which they are bonded form a six-
 10 membered heterocyclic ring whose heteroatom, X, is O,
 S, S(O), S(O₂) or NR⁵, e.g., a 4-piperidinyl,
 tetrahydropyranyl or tetrahydrothiopyranyl group.
 The nitrogen atom of the 4-piperidinyl group is
 substituted with a moiety R⁵ selected from the group
 15 consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆
 cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and a
 sulfonyl C₁-C₄ hydrocarbyl group. Those preferred
 compounds correspond in structure generally and
 specifically to Formulas VIII and IX, respectively,
 20 below

-36-



The word "hydrocarbyl" is used herein as a short hand term to include straight and branched chain aliphatic as well as alicyclic groups or radicals that contain only carbon and hydrogen. Thus, alkyl, alkenyl and alkynyl groups are contemplated, whereas aromatic hydrocarbons such as phenyl and naphthyl groups, which strictly speaking are also hydrocarbyl groups, are referred to herein as aryl groups or radicals, as discussed hereinafter. Where a specific aliphatic hydrocarbyl substituent group is intended, that group is recited; i.e., C₁-C₄ alkyl, methyl or dodecanyl. Exemplary hydrocarbyl groups contain a chain of 1 to about 12 carbon atoms, and preferably one to about 10 carbon atoms.

A particularly preferred hydrocarbyl group is an alkyl group. As a consequence, a generalized, but more preferred substituent can be recited by replacing the descriptor "hydrocarbyl" with "alkyl" in any of the substituent groups enumerated herein.

Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. Examples of suitable alkenyl radicals include ethenyl (vinyl), 2-propenyl, 3-propenyl, 1,4-

-37-

pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, decenyl and the like. Examples of alkynyl radicals include ethynyl, 2-propynyl, 3-propynyl, decynyl; 1-butynyl, 2-butynyl, 3-butynyl, and the
5 like.

Usual chemical suffix nomenclature is followed when using the word "hydrocarbyl" except that the usual practice of removing the terminal "yl" and adding an appropriate suffix is not always
10 followed because of the possible similarity of a resulting name to one or more substituents. Thus, a hydrocarbyl ether is referred to as a "hydrocarbyloxy" group rather than a "hydrocarboxy" group as may possibly be more proper when following
15 the usual rules of chemical nomenclature. On the other hand, a hydrocarbyl group containing a carbonyl group is referred to as a hydrocarboyl group inasmuch as there is no ambiguity in using that suffix. As a skilled worker will understand, a substituent that
20 cannot exist such as a C₁ alkenyl group is not intended to be encompassed by the word "hydrocarbyl".

The term "carbonyl", alone or in combination, means a -C(=O)- group wherein the remaining two bonds (valences) are independently substituted. The term "thiol" or "sulfhydryl", alone or in combination, means a -SH group. The term "thio" or "thia", alone or in combination, means a thiaether group; i.e., an ether group wherein the ether oxygen is replaced by a sulfur atom.
25

The term "amino", alone or in combination, means an amine or -NH₂ group, whereas the term mono-substituted amino, alone or in combination, means a substituted amine -N(H)(substituent) group wherein
30

-38-

one hydrogen atom is replaced with a substituent, and disubstituted amine means a -N(substituent)₂ wherein two hydrogen atoms of the amino group are replaced with independently selected substituent groups.

5 Amines, amino groups and amides are classes that can be designated as primary (I°), secondary (II°) or tertiary (III°) or unsubstituted, mono-substituted or di-substituted depending on the degree of substitution of the amino nitrogen. Quaternary amine
10 (IV°) means a nitrogen with four substituents (- $\text{N}^+(\text{substituent})_4$) that is positively charged and accompanied by a counter ion or N-oxide means one substituent is oxygen and the group is represented as (- $\text{N}^+(\text{substituent})_3\text{-O}^-$); i.e., the charges are
15 internally compensated.

The term "cyano", alone or in combination, means a -C-triple bond-N (-CN) group. The term "azido", alone or in combination, means a -N-double bond-N-double bond-N- (-N=N=N-) group.

20 The term "hydroxyl", alone or in combination, means a -OH group. The term "nitro", alone or in combination, means a -NO₂ group.

The term "azo", alone or in combination, means a -N=N- group wherein the bonds at the terminal
25 positions are independently substituted. The term "hydrazino", alone or in combination, means a -NH-NH- group wherein the remaining two bonds (valences) are independently substituted. The hydrogen atoms of the hydrazino group can be replaced, independently, with
30 substituents and the nitrogen atoms can form acid addition salts or be quaternized.

-39-

The term "sulfonyl", alone or in combination, means a $-S(O)_2-$ group wherein the remaining two bonds (valences) can be independently substituted. The term "sulfoxido", alone or in combination, means a $-S(=O)_1-$ group wherein the remaining two bonds (valences) can be independently substituted. The term "sulfonylamide", alone or in combination, means a $-S(=O)_2-N=$ group wherein the remaining three bonds (valences) are independently substituted. The term "sulfinamido", alone or in combination, means a $-S(=O)_1N=$ group wherein the remaining three bonds (valences) are independently substituted. The term "sulfenamide", alone or in combination, means a $-S-N=$ group wherein the remaining three bonds (valences) are independently substituted.

The term "hydrocarbyloxy", alone or in combination, means an hydrocarbyl ether radical wherein the term hydrocarbyl is as defined above. Examples of suitable hydrocarbyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like. The term "cyclohydrocarbyl", alone or in combination, means a hydrocarbyl radical that contains 3 to about 8 carbon atoms, preferably from about 3 to about 6 carbon atoms, and is cyclic. The term "cyclohydrocarbylhydrocarbyl" means an hydrocarbyl radical as defined above which is substituted by a cyclohydrocarbyl as also defined above. Examples of such cyclohydrocarbylhydrocarbyl radicals include cyclopropyl, cyclobutyl, cyclopentenyl, cyclohexyl cyclooctynyl and the like.

-40-

The term "aryl", alone or in combination, means a phenyl or naphthyl radical that optionally carries one or more substituents selected from hydrocarbyl, hydrocarbyloxy, halogen, hydroxy, amino, 5 nitro and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, and the like. The term "arylhydrocarbyl", alone or in combination, means an hydrocarbyl radical as defined above in 10 which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl and the like. The term "arylhydrocarbyloxycarbonyl", alone or in combination, means a radical of the formula -C(O)-O- 15 arylhydrocarbyl in which the term "arylhydrocarbyl" has the significance given above. An example of an arylhydrocarbyloxycarbonyl radical is benzyloxycarbonyl. The term "aryloxy" means a radical of the formula aryl-O- in which the term aryl 20 has the significance given above. The term "aromatic ring" in combinations such as substituted-aromatic ring sulfonamide, substituted-aromatic ring sulfinamide or substituted-aromatic ring sulfenamide means aryl or heteroaryl as defined above.

25 The terms "hydrocarbyloyl" or "hydrocarbylcarbonyl", alone or in combination, mean an acyl radical derived from an hydrocarbylcarboxylic acid, examples of which include acetyl, propionyl, acryloyl, butyryl, valeryl, 4-methylvaleryl, and the 30 like. The term "cyclohydrocarbylcarbonyl" means an acyl group derived from a monocyclic or bridged cyclohydrocarbylcarboxylic acid such as cyclopropanecarbonyl, cyclohexenecarbonyl,

-41-

adamantanecarbonyl, and the like, or from a benz-fused monocyclic cyclohydrocarbylcarboxylic acid that is optionally substituted by, for example, a hydrocarbyloylamino group, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The terms "arylhydrocarbyloyl" or "arylhydrocarbylcarbonyl" mean an acyl radical derived from an aryl-substituted hydrocarbylcarboxylic acid such as phenylacetyl, 3-phenylpropenyl (cinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminocinnamoyl, 4-methoxycinnamoyl and the like.

The terms "aroyl" or "arylcarbonyl" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 2-naphthoyl, 6-carboxy-2-naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like.

The heterocyclyl (heterocyclo) or heterocyclohydrocarbyl portion of a heterocyclylcarbonyl, heterocyclloxycarbonyl, heterocyclhydrocarbyloxycarbonyl, or heterocyclohydrocarbyl group or the like is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle that contains one to four hetero atoms selected from nitrogen, oxygen and sulphur, which is optionally substituted on one or more carbon atoms by a halogen, alkyl, alkoxy, oxo group, and the like, and/or on a secondary nitrogen

-42-

- atom (i.e., -NH-) by an hydrocarbyl, arylhydrocarbyloxycarbonyl, hydrocarbyloyl, aryl or arylhydrocarbyl or on a tertiary nitrogen atom (i.e. =N-) by oxido and that is attached via a carbon atom.
- 5 The tertiary nitrogen atom with three substituents can also form a N-oxide [=N(O)-] group. Examples of such heterocyclyl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, and the like.
- 10 The heteroaryl portion of a heteroaroyl, heteroaryloxycarbonyl, or a heteroarylhydrocarbyloyl (heteroarylhydrocarbyl carbonyl) group or the like is an aromatic monocyclic, bicyclic, or tricyclic heterocycle that contains the hetero atoms and is
- 15 optionally substituted as defined above with respect to the definition of heterocyclyl. A "heteroaryl" group is an aromatic heterocyclic ring substituent that can contain one, two, three or four atoms in the ring that are other than carbon. Those heteroatoms
- 20 can be nitrogen, sulfur or oxygen. A heteroaryl group can contain a single five- or 6-membered ring or a fused ring system that contains two 6-membered rings or a five- and a 6-membered ring. Exemplary heteroaryl groups include 6-membered ring
- 25 substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as 1,3,5-, 1,2,4- or 1,2,3-triazinyl, imidazyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-
- 30 oxadiazolyl and isothiazolyl groups ; six/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl and anthranilyl groups ; and six/6-membered

-43-

fused rings such as 1,2-, .1,4-, .2,3- and 2,1-benzopyranyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl groups.

The term "cyclohydrocarbylhydrocarbyloxy-carbonyl" means an acyl group derived from a cyclohydrocarbylhydrocarbyloxycarboxylic acid of the formula cyclohydrocarbylhydrocarbyl-O-COOH wherein cyclohydrocarbylhydrocarbyl has the significance given above. The term "aryloxyhydrocarbyloyl" means an acyl radical of the formula aryl-O-hydrocarbyloyl wherein aryl and hydrocarbyloyl have the significance given above. The term "heterocycloloxycarbonyl" means an acyl group derived from heterocyclol-O-COOH wherein heterocyclol is as defined above. The term "heterocyclolhydrocarbyloyl" is an acyl radical derived from a heterocyclol-substituted hydrocarbylcarboxylic acid wherein heterocyclol has the significance given above. The term "heterocyclolhydrocarbyloxycarbonyl" means an acyl radical derived from a heterocyclol-substituted hydrocarbyl-O-COOH wherein heterocyclol has the significance given above. The term "heteroaryloxy carbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the significance given above.

The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amino-substituted carboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, hydrocarbyl, aryl, aralkyl, cyclohydrocarbyl,

-44-

cyclohydrocarbylhydrocarbyl radicals and the like. The term "aminohydrocarbyloyl" means an acyl group derived from an amino-substituted hydrocarbylcarboxylic acid wherein the amino group 5 can be a primary, secondary or tertiary amino group containing substituents independently selected from hydrogen, alkyl, aryl, aralkyl, cyclohydrocarbyl, cyclohydrocarbylhydrocarbyl radicals and the like.

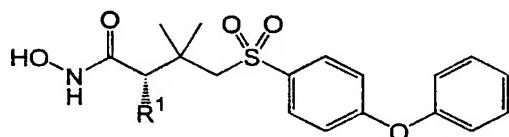
The term "halogen" means fluorine, 10 chlorine, bromine or iodine. The term "halohydrocarbyl" means a hydrocarbyl radical having the significance as defined above wherein one or more hydrogens are replaced with a halogen. Examples of such halohydrocarbyl radicals include chloromethyl, 15 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like. The term perfluorohydrocarbyl means a hydrocarbyl group wherein each hydrogen has been replaced by a fluorine atom. Examples of such perfluorohydrocarbyl 20 groups, in addition to trifluoromethyl above, are perfluorobutyl, perfluoroisopropyl, perfluorododecyl and perfluorodecyl.

Table 1 through Table 37, below, show several contemplated N-hydroxy sulfonyl butanamide 25 compounds as structural formulas that illustrate substituent groups. Each group of compounds is illustrated by a generic formula, followed by a series of preferred moieties or groups that constitute various substituents that can be attached 30 at the position clearly shown in the generic structure. The substituent symbols, e.g., R¹, are as shown in each Table. One bond (straight line) is shown with those substituents to indicate the

-45-

respective positions of attachment in the illustrated compound. This system is well known in the chemical communication arts and is widely used in scientific papers and presentations.

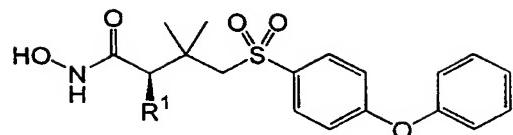
Table 1



Example	---R^1	Example	---R^1
1		9	
2		10	
3			
4			
5			
6			
7			
8			

- 46 -

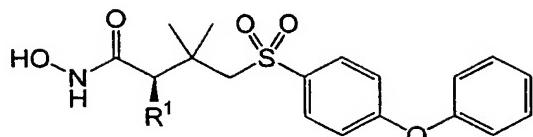
Table 2



Example	—R ¹	Example	—R ¹
1		9	
2		10	
3			
4			
5			
6			
7			
8			

-47-

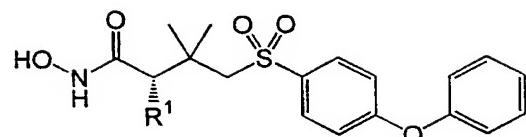
Table 3



Example	—R ¹	Example	—R ¹
1		10	
2		11	
3		12	
4		13	
5		14	
6			
7			
8			
9		15	

- 48 -

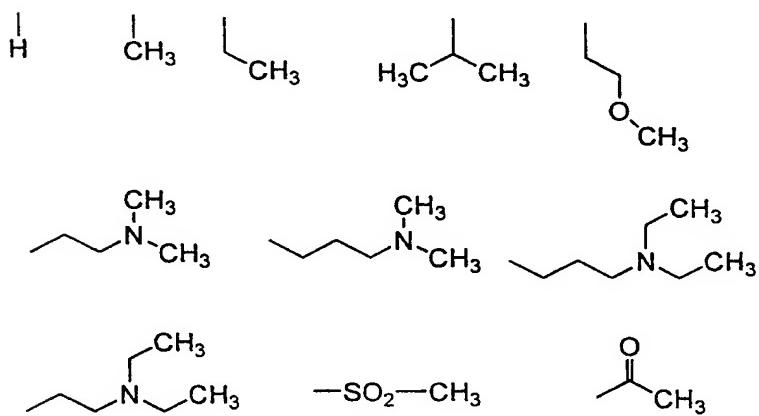
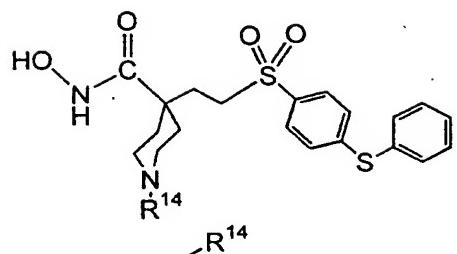
Table 4



Example	—R ¹	Example	—R ¹
1		10	
2		11	
3		12	
4		13	
5		14	
6			
7			
8			
9		15	

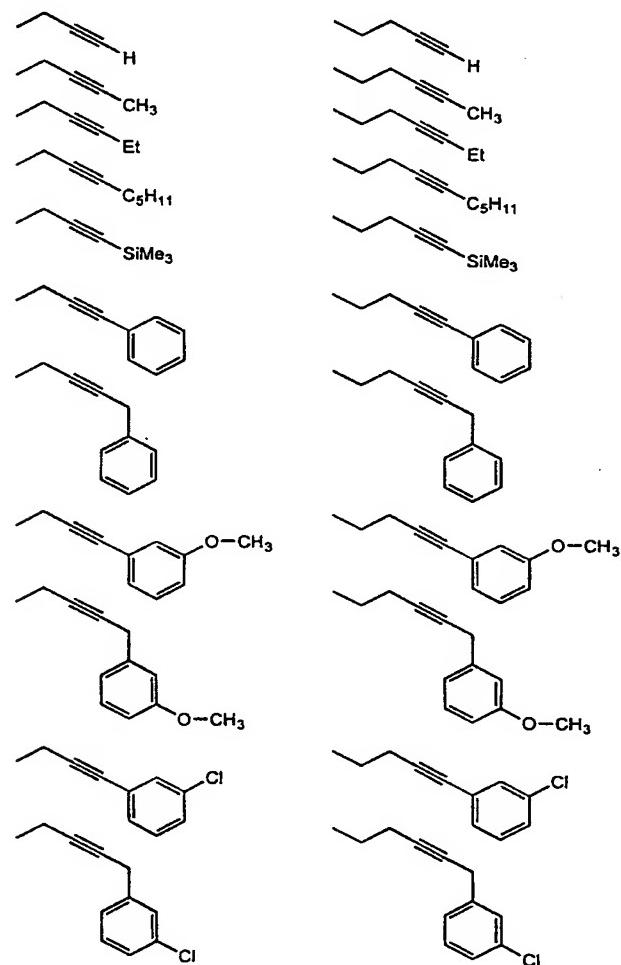
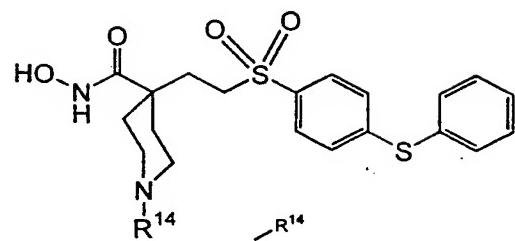
- 49 -

Table 5



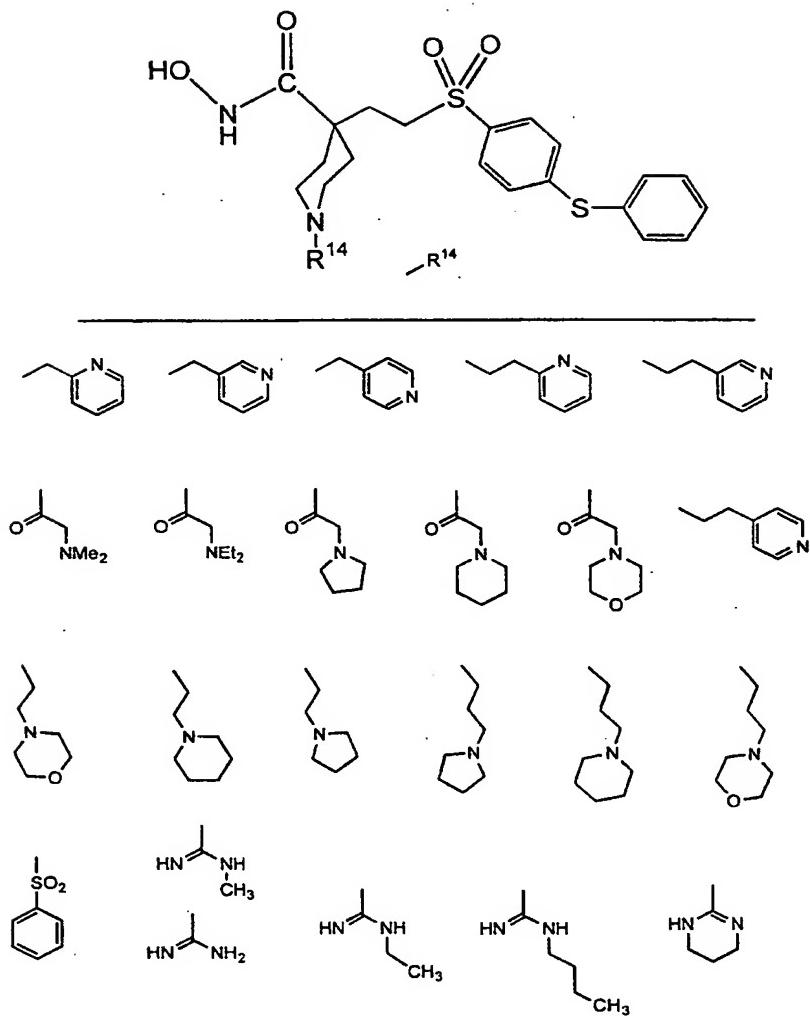
- 50 -

Table 6



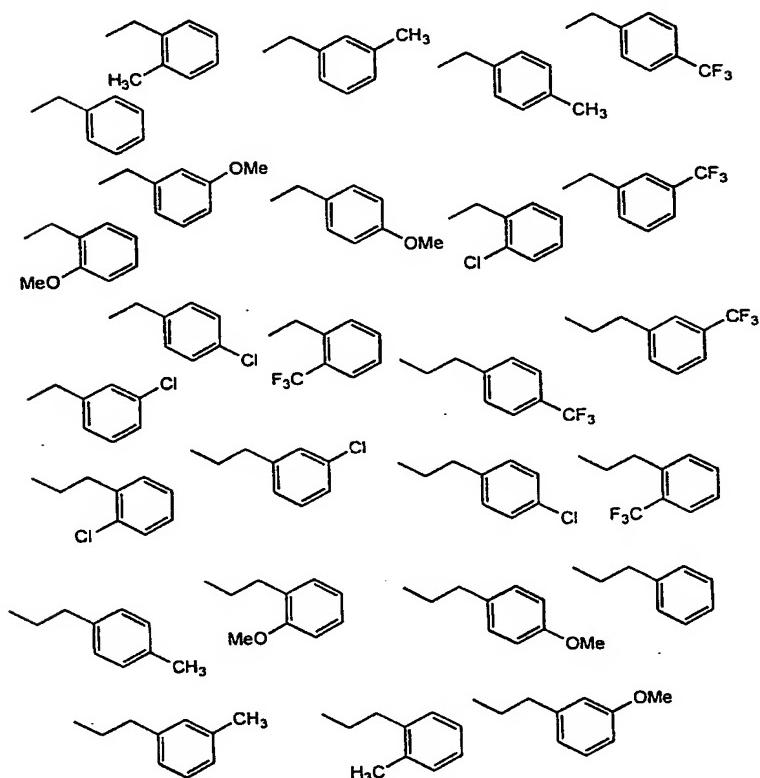
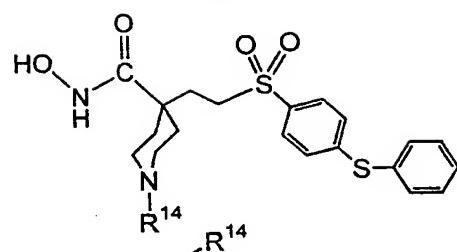
-51-

Table 7

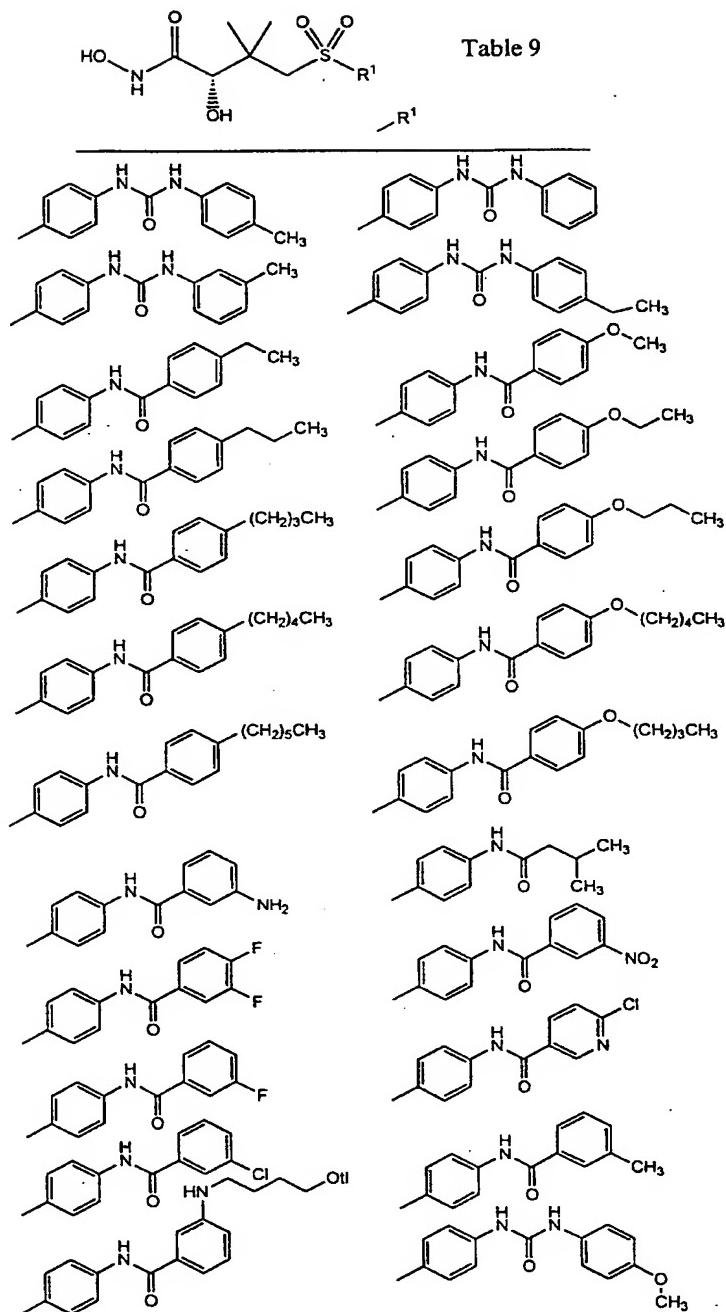


- 52 -

Table 8

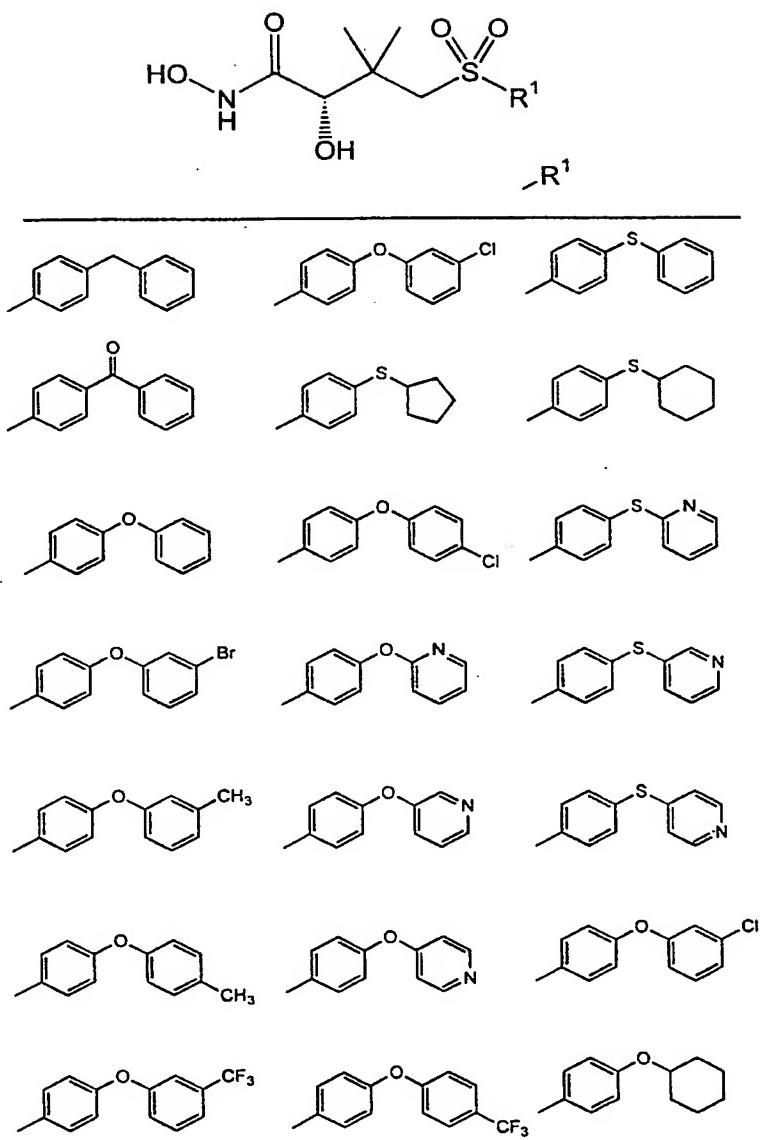


- 53 -



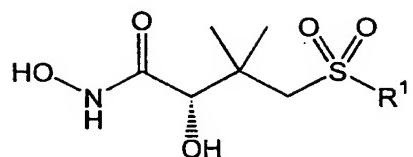
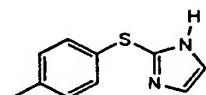
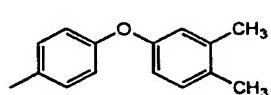
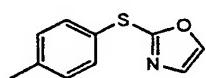
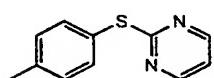
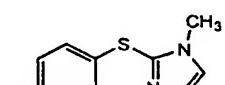
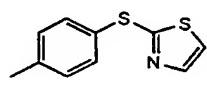
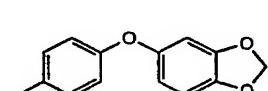
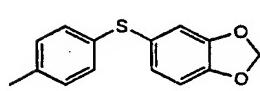
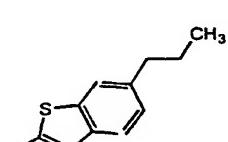
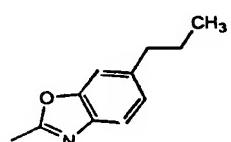
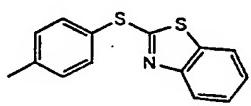
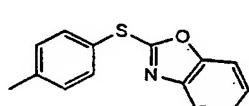
- 54 -

Table 10



-55-

Table 11

 R^1 

- 56 -

Table 12

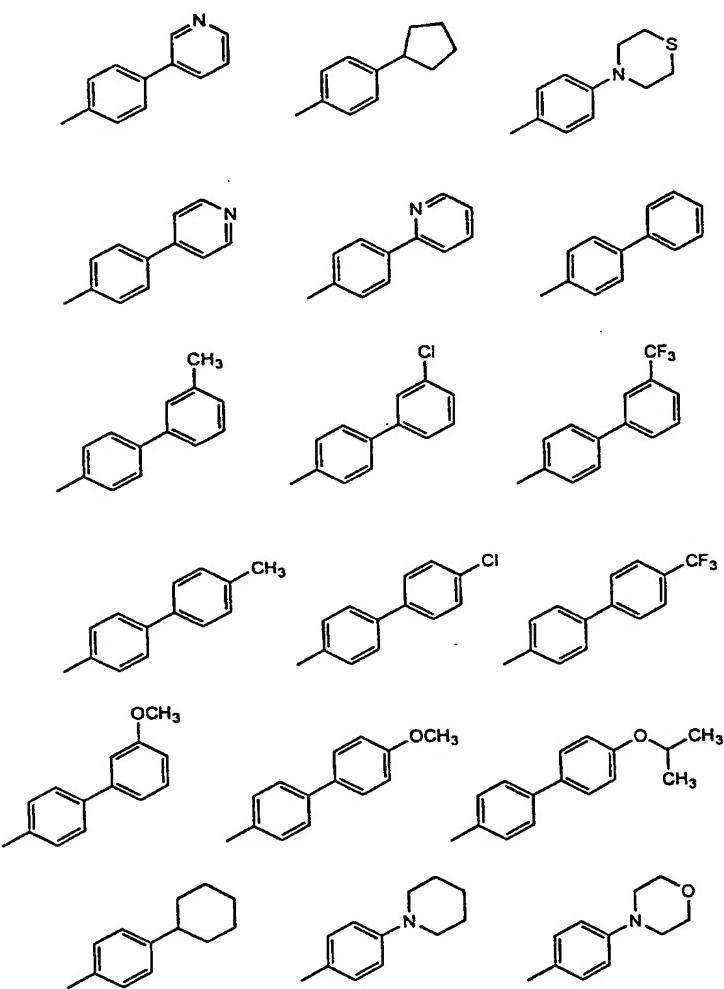
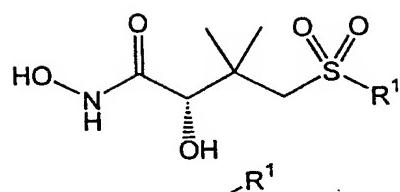
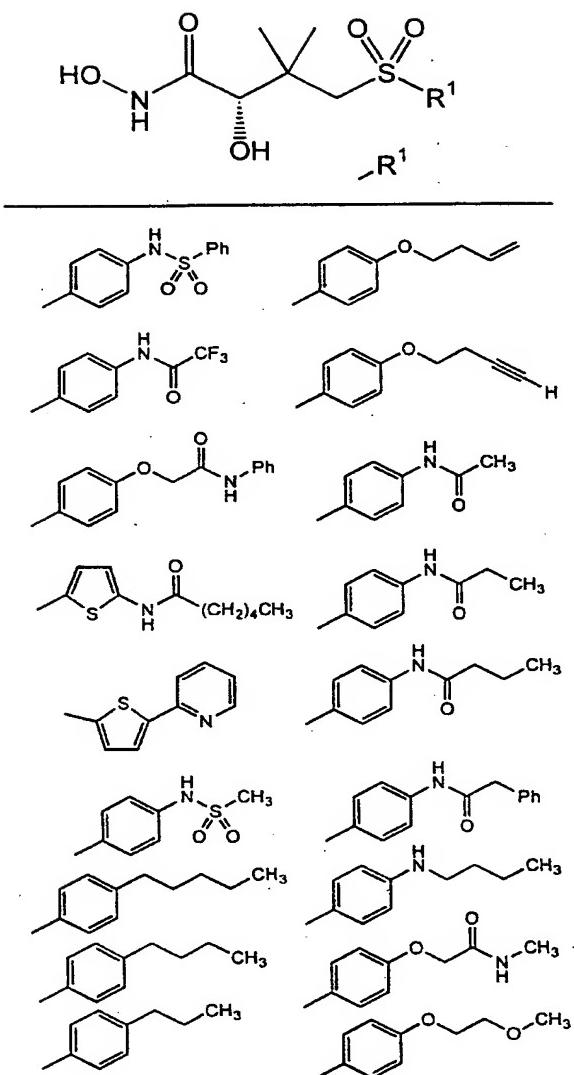


Table 13



- 58 -

Table 14

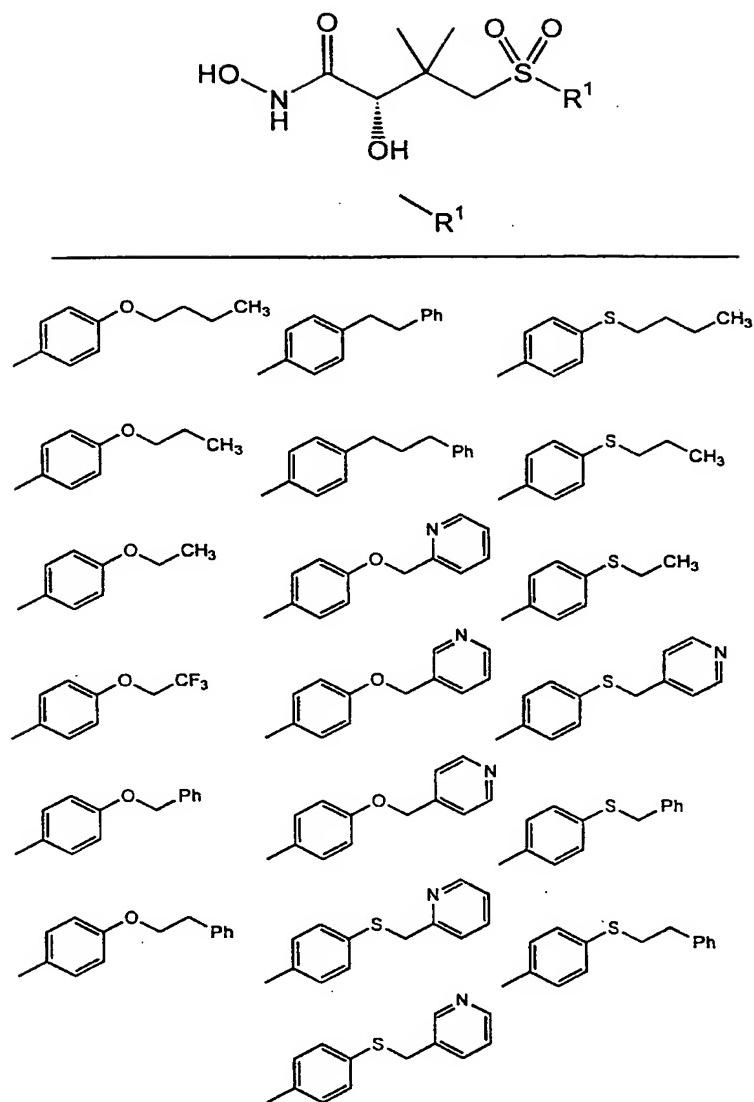
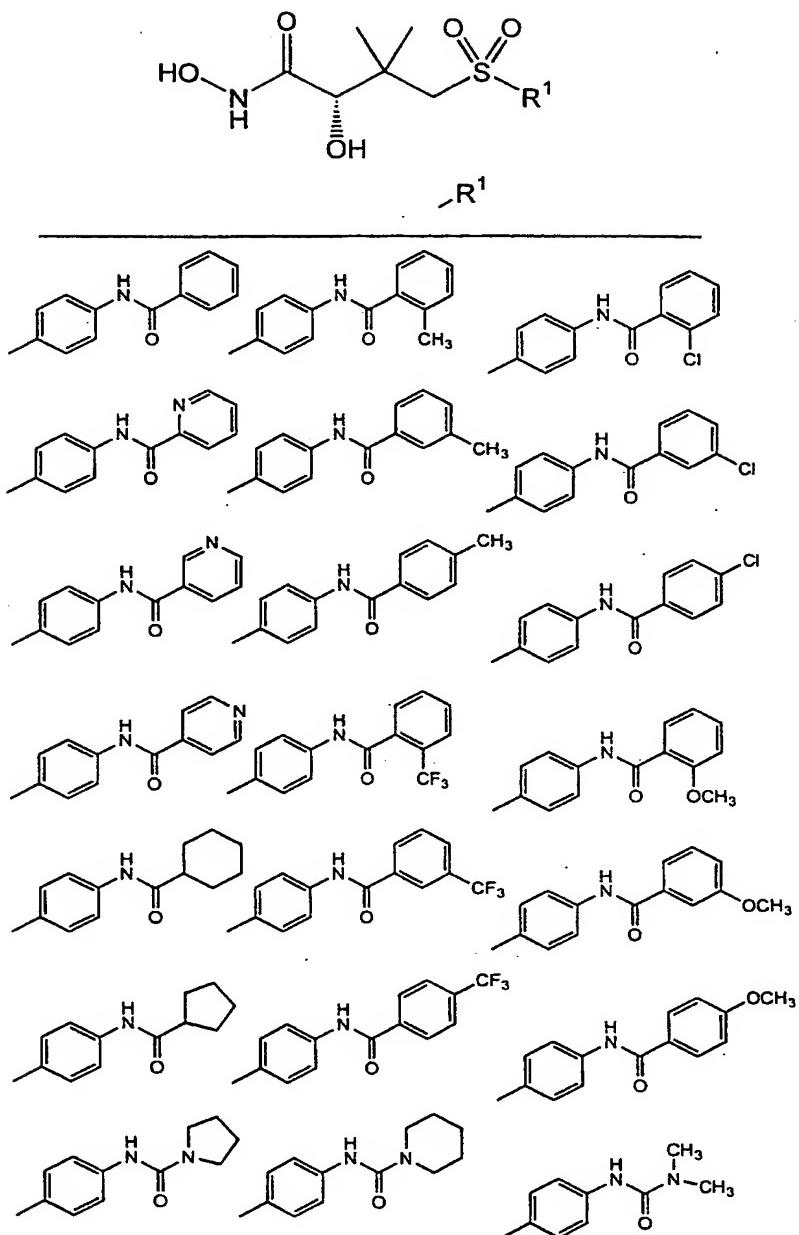
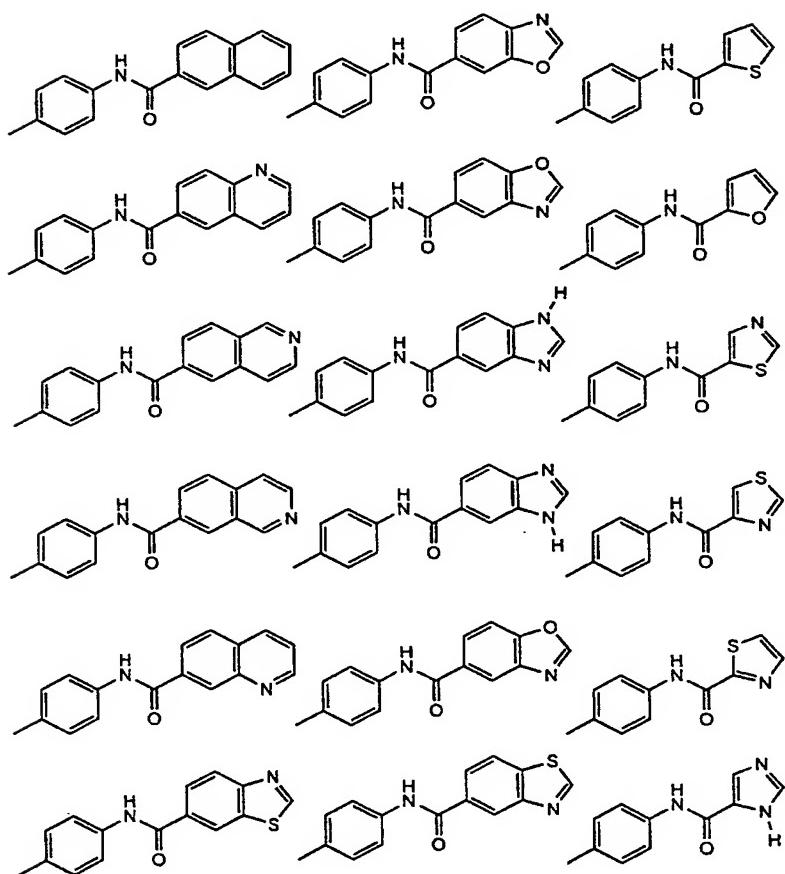
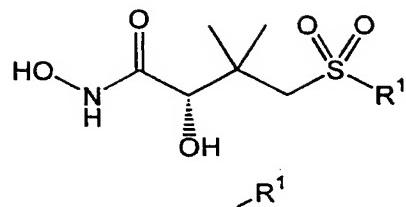


Table 15



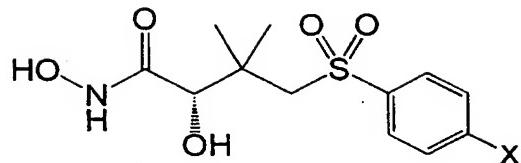
- 60 -

Table 16



- 61 -

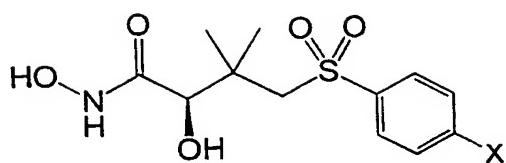
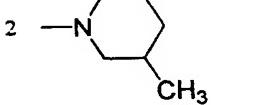
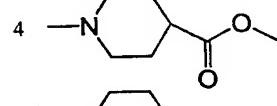
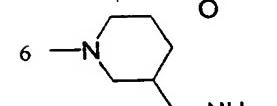
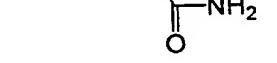
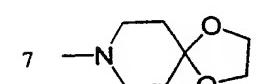
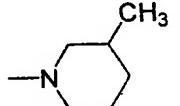
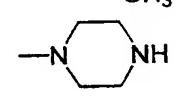
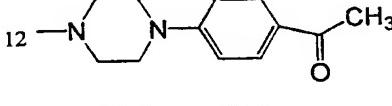
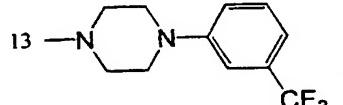
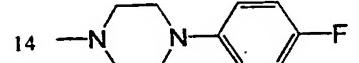
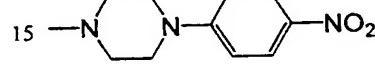
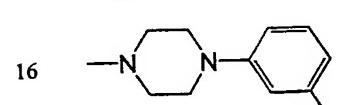
Table 17



Example	—X	Example	—X
1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

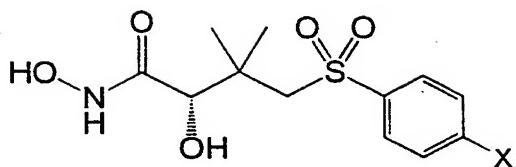
- 62 -

Table 18

	
Example	—X
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	

- 63 -

Table 19



Example	X	Example	X
1		7	
2		8	
3		9	
4		10	
5		11	
6			

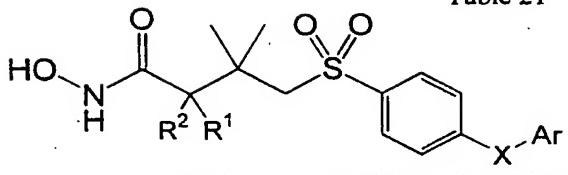
- 64 -

Table 20

Example	R ¹	R ²	Example	R ¹	R ²
1	-H	-H	12		
2	-H	-CH ₃	13		
3	-CH ₃	-CH ₃	14		
4	-H	-OH	15		
5	-CH ₃	-OH	16		
6	-CH ₃	-NH ₂	17		
7			18		
8			19		
9			20		
10			21		
11			22		

-65-

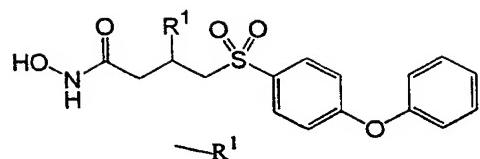
Table 21



Example	R ¹	R ²	X	Ar
1			O	
2			O	
3			O	
4			O	
5			O	
6			O	
7			O	
8			O	
9			S	
10			S	

- 66 -

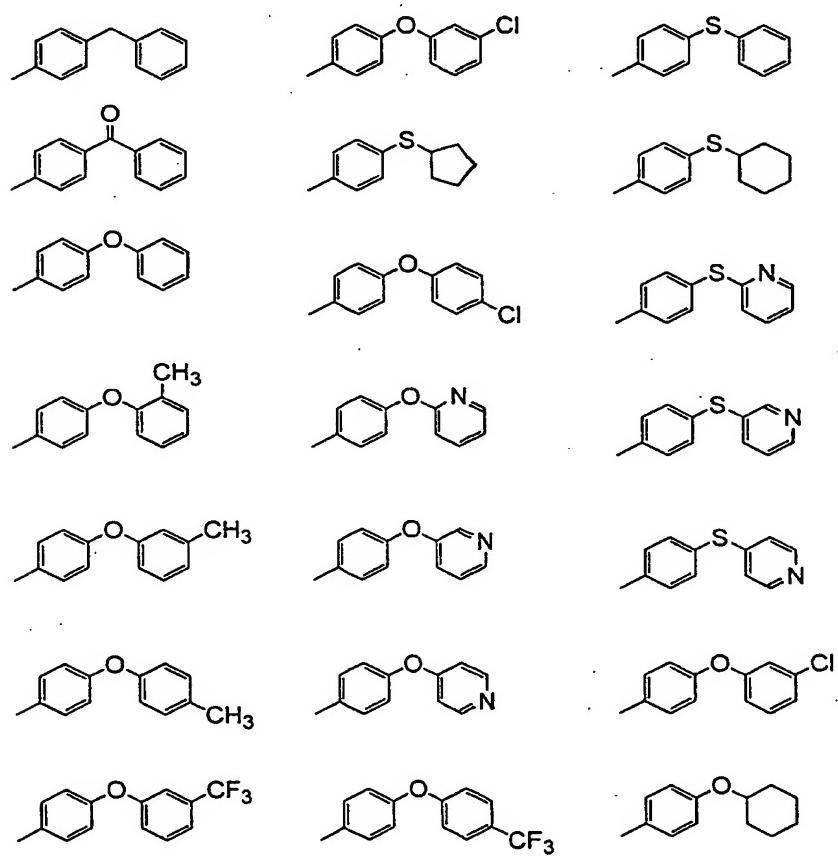
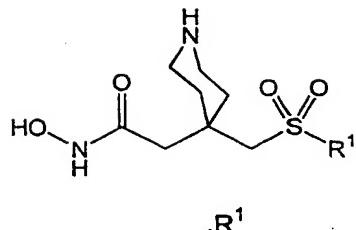
Table 22



Example	---R^1	Example	---R^1
1		9	
2		10	
3			
4			
5			
6			
7			
8			

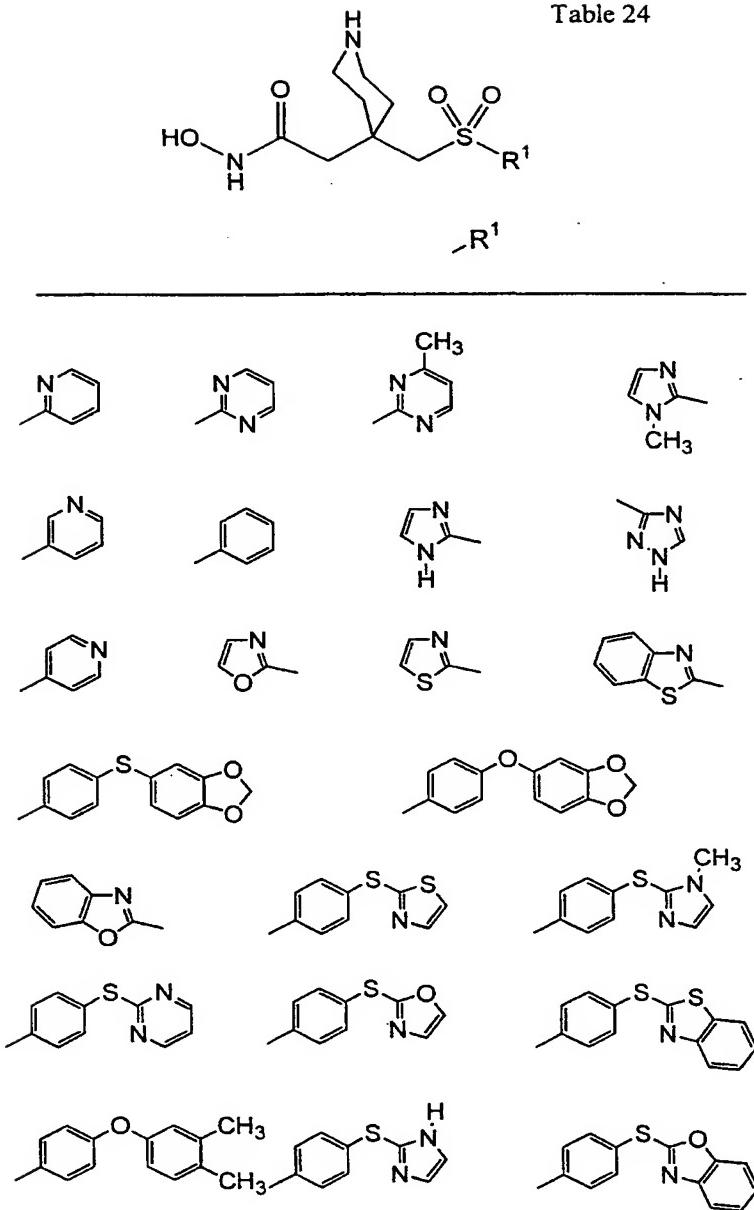
- 67 -

Table 23



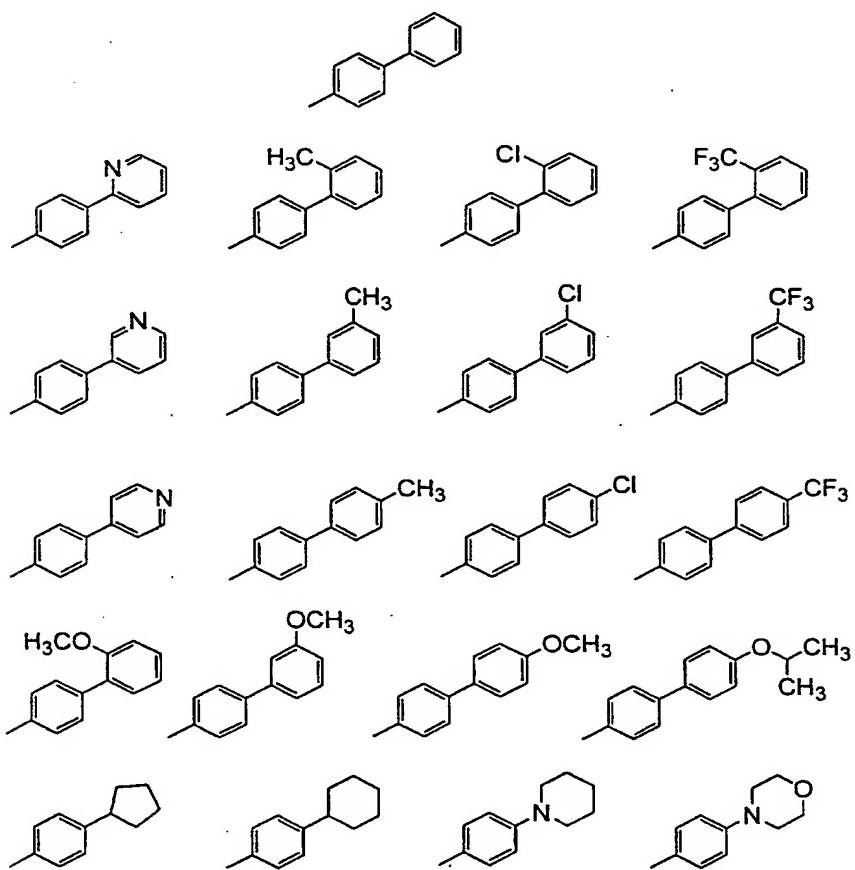
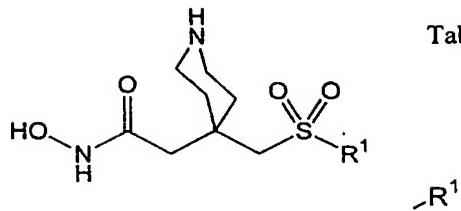
- 68 -

Table 24



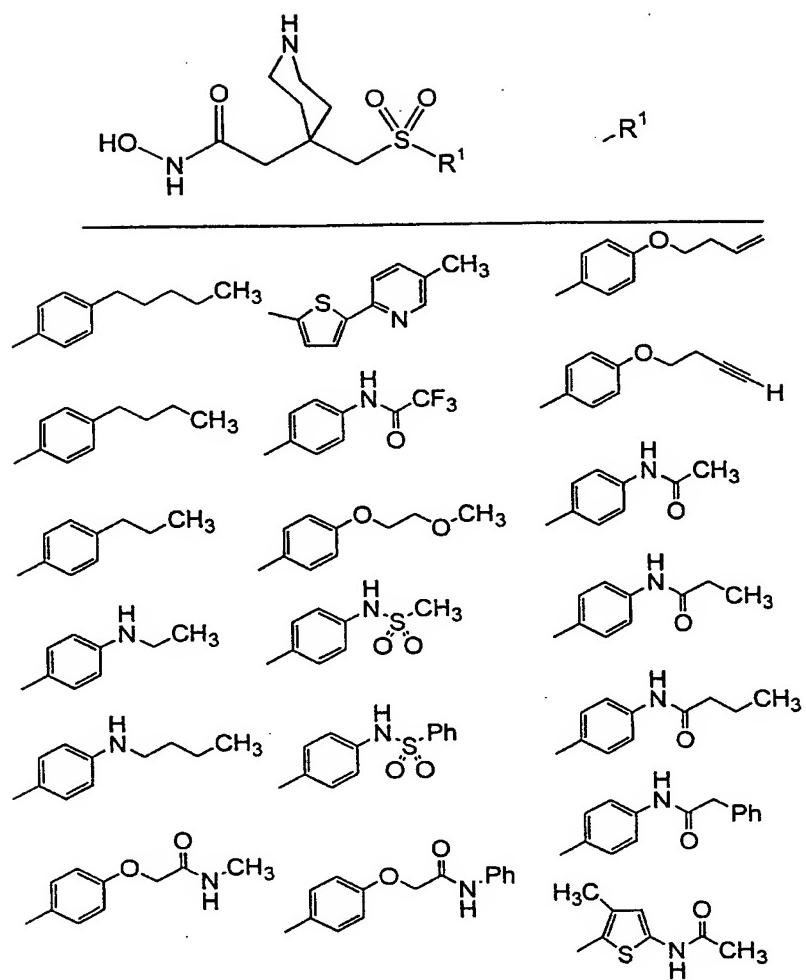
- 69 -

Table 25



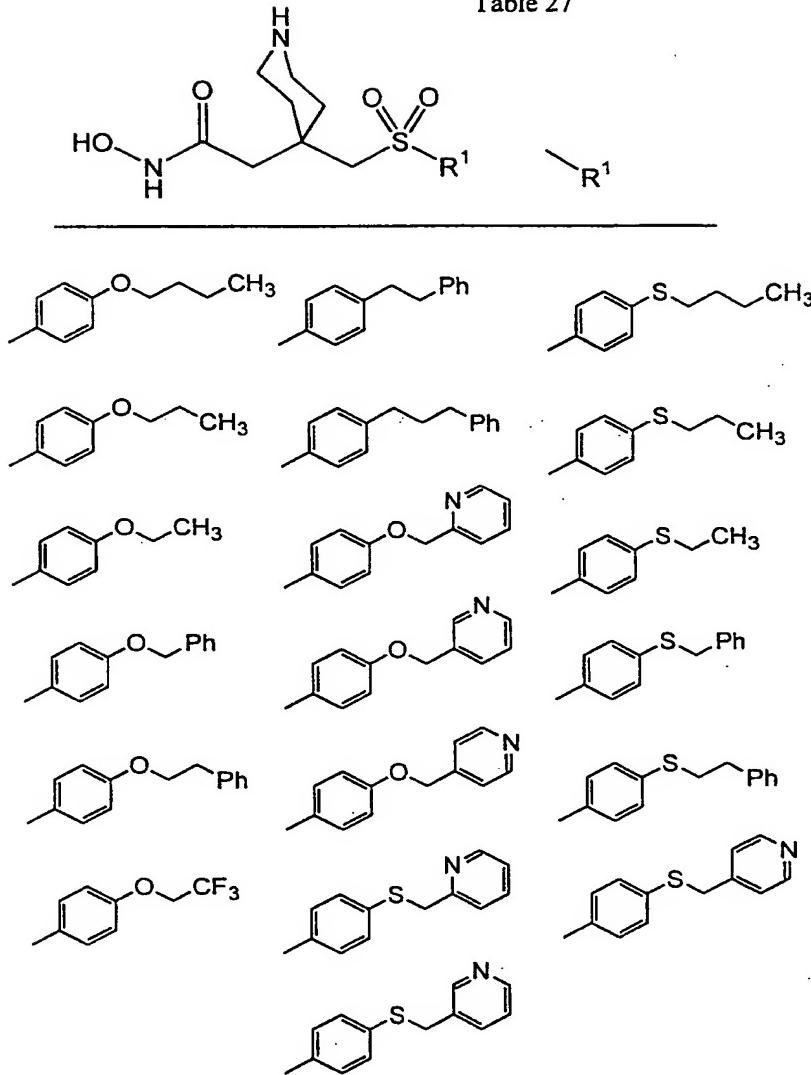
- 70 -

Table 26



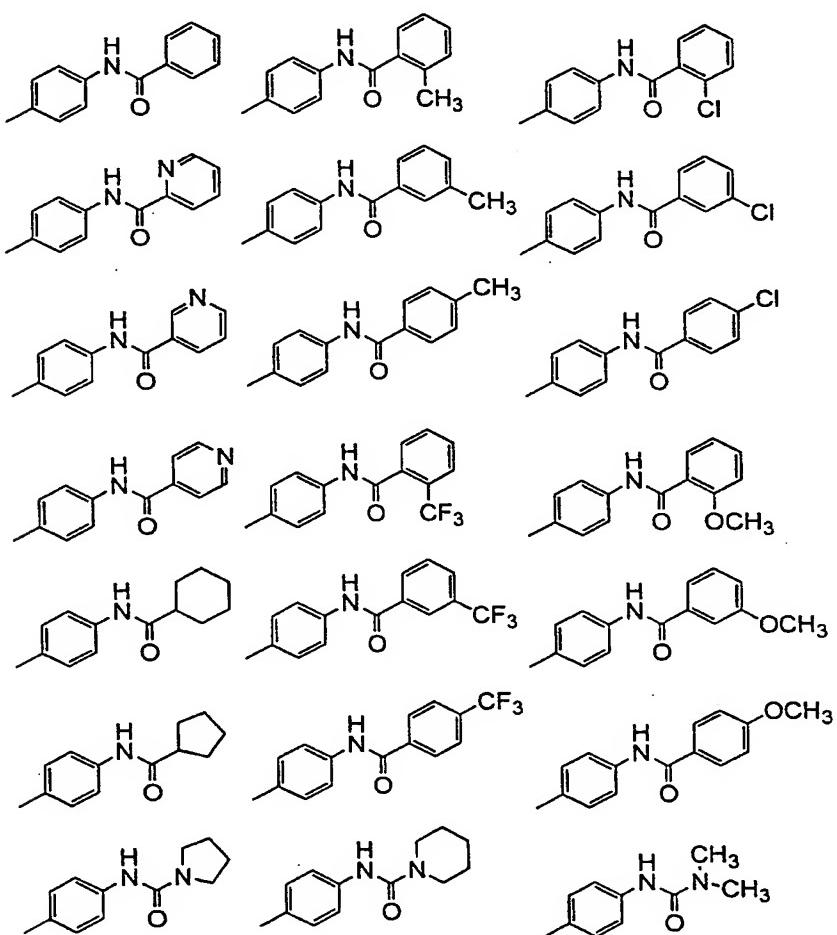
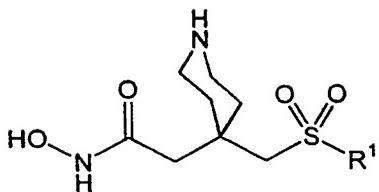
-71-

Table 27



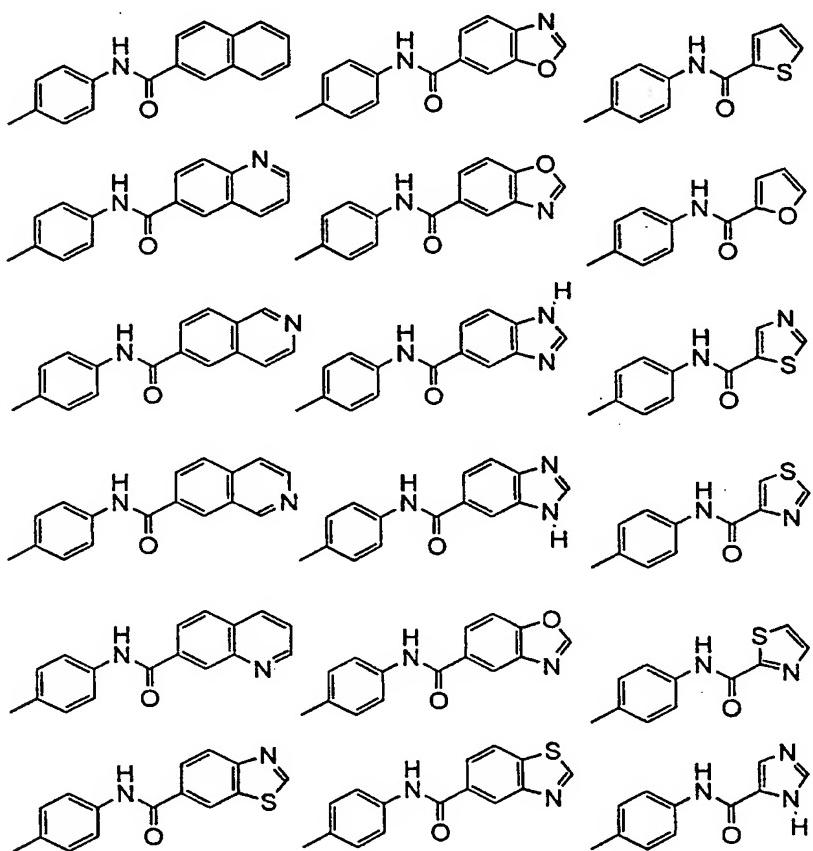
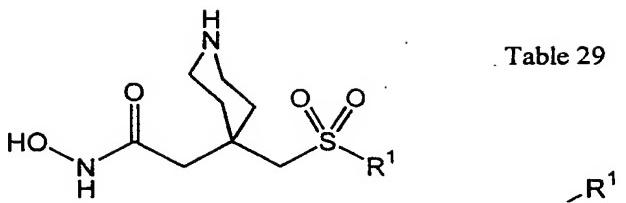
- 72 -

Table 28

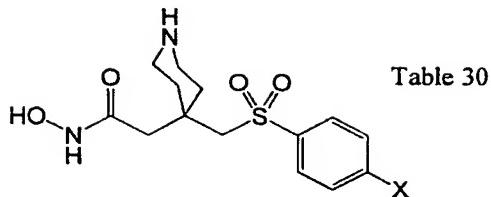


- 73 -

Table 29



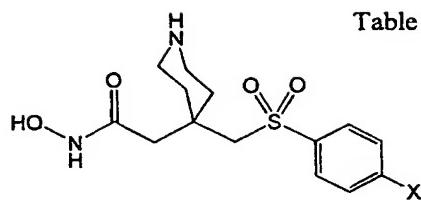
- 74 -



Example	X	Example	X
1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

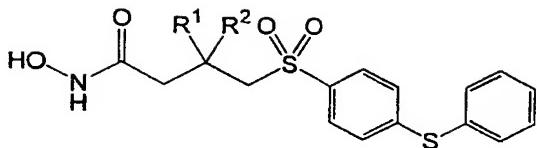
- 75 -

Table 31



Example	X	Example	X
1		8	
2		9	
3		10	
4		11	
5			
6			
7			

Table 32



Example	R ¹	R ²	Example	R ¹	R ²	Example	R ¹	R ²
1	-H	-H	12			18		
2	-H	-CH ₃	13			19		
3	-CH ₃	-CH ₃	14			20		
4	-H	-OH	15			21		
5	-CH ₃	-OH	16			22		
6	-CH ₃	-NH ₂	17					
7								
8								
9								
10								
11								

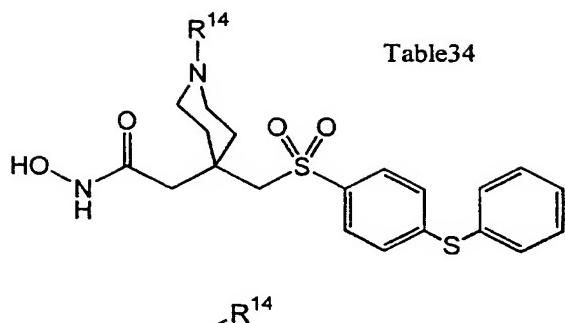
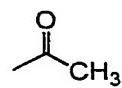
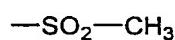
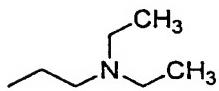
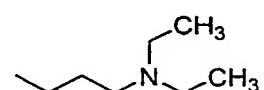
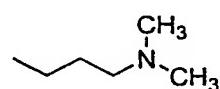
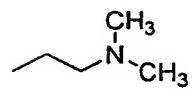
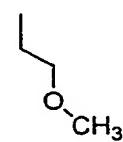
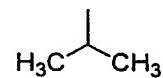
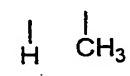
-77-

Table 33

Example	---R^1	Example	---R^1
1		10	
2		11	
3		12	
4		13	
5		14	
6			
7			
8			
9		15	

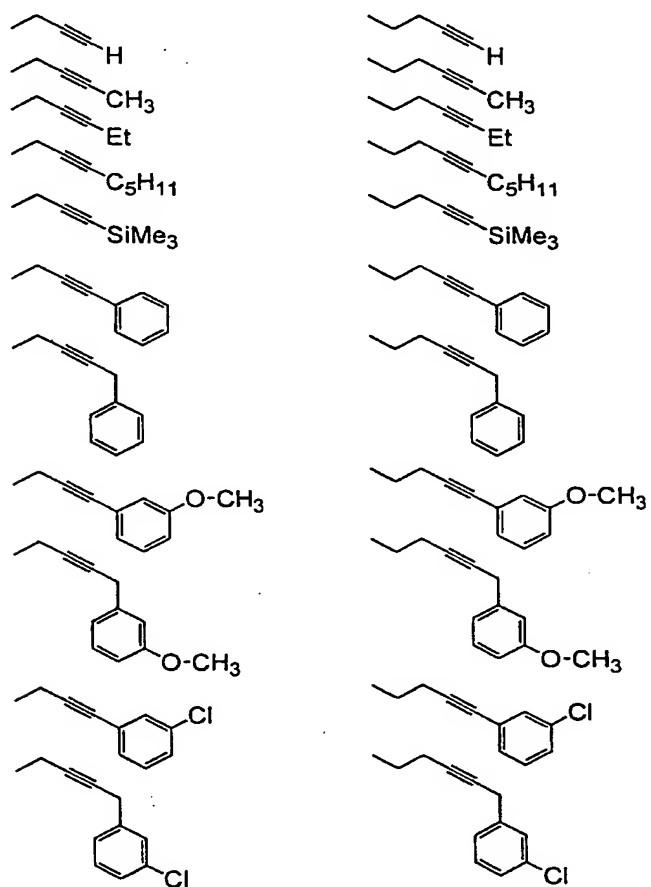
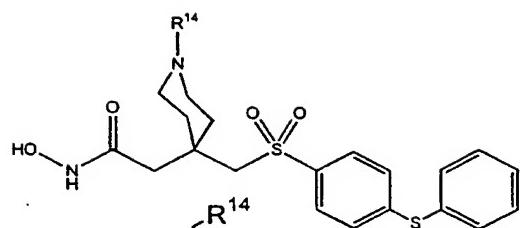
- 78 -

Table 34

 -R^{14} 

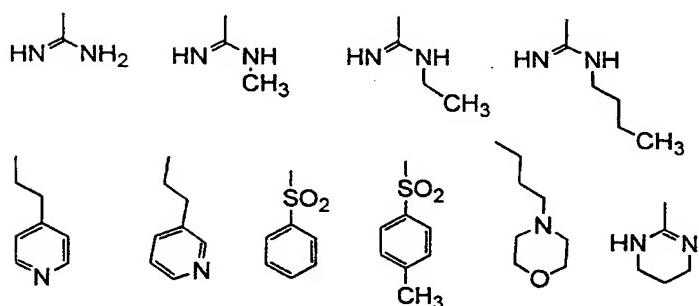
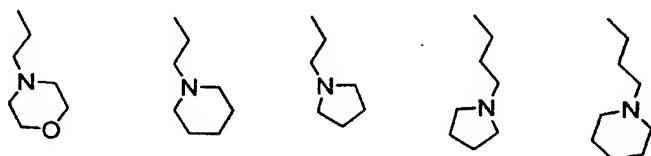
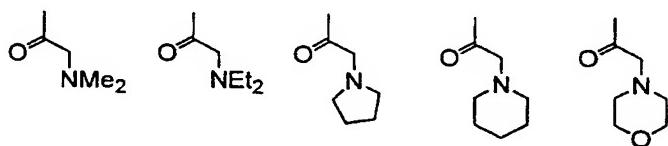
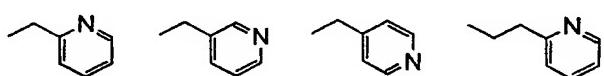
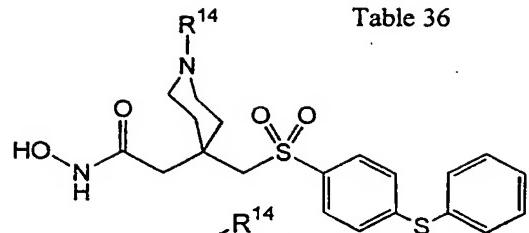
- 79 -

Table 35



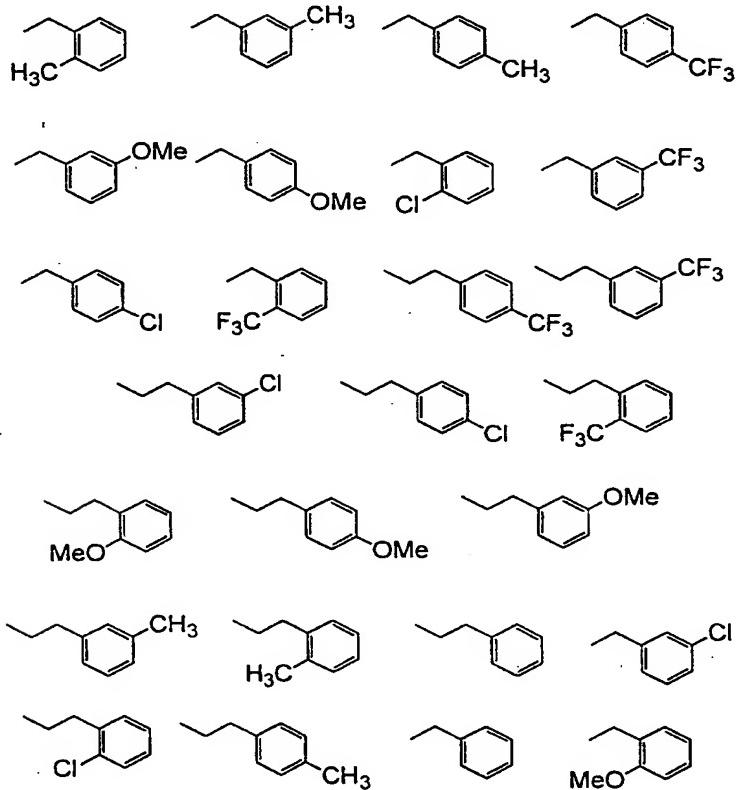
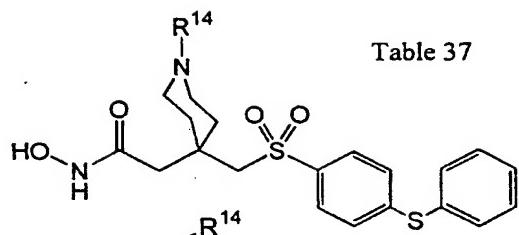
- 80 -

Table 36



- 81 -

Table 37

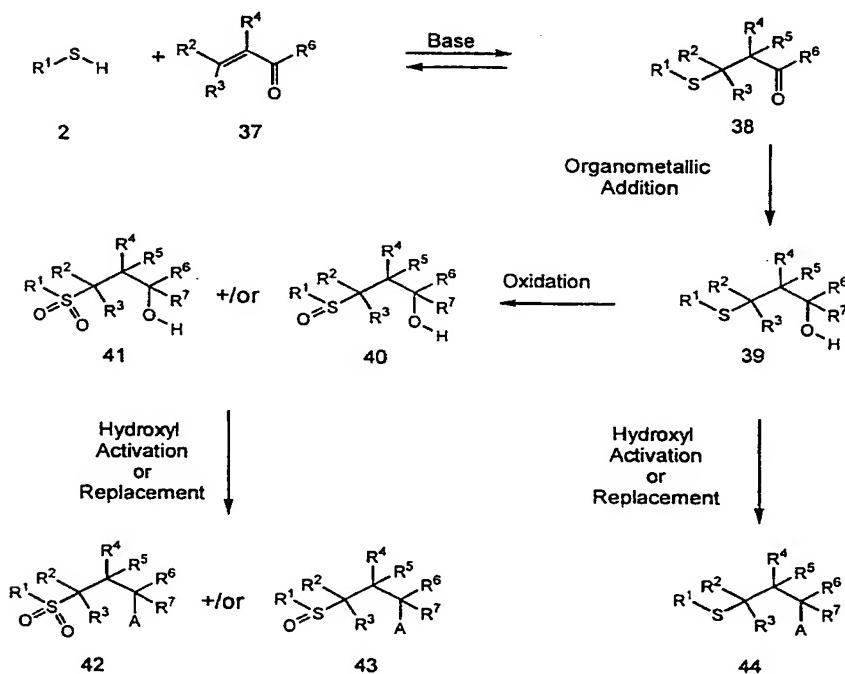


-82-

Preparation of Useful Compounds

Compounds of the invention can be produced in accordance with the following generic synthetic Schemes A-D. It is noted that the numbers shown on R groups in these schemes, except in Scheme D, are different from those utilized in structural formulas having Roman numerals. That difference in numbering is to illustrate the generality of these synthesis schemes. Specific synthetic schemes that illustrate the preparation of specific compounds follow hereinafter.

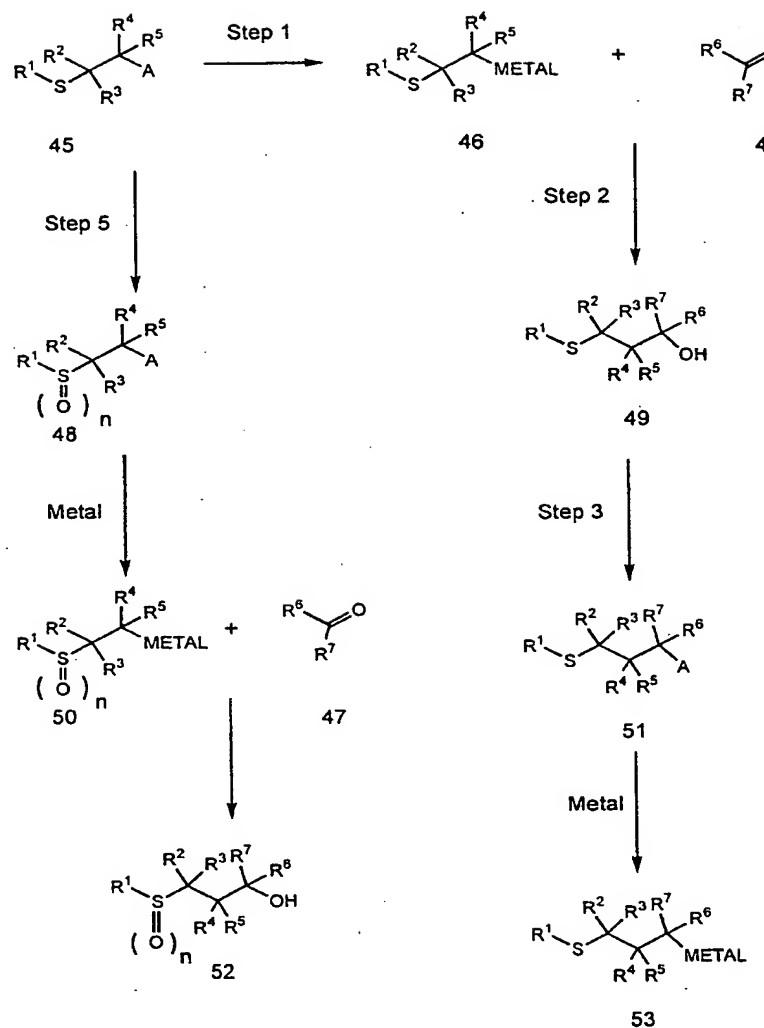
SCHEME A



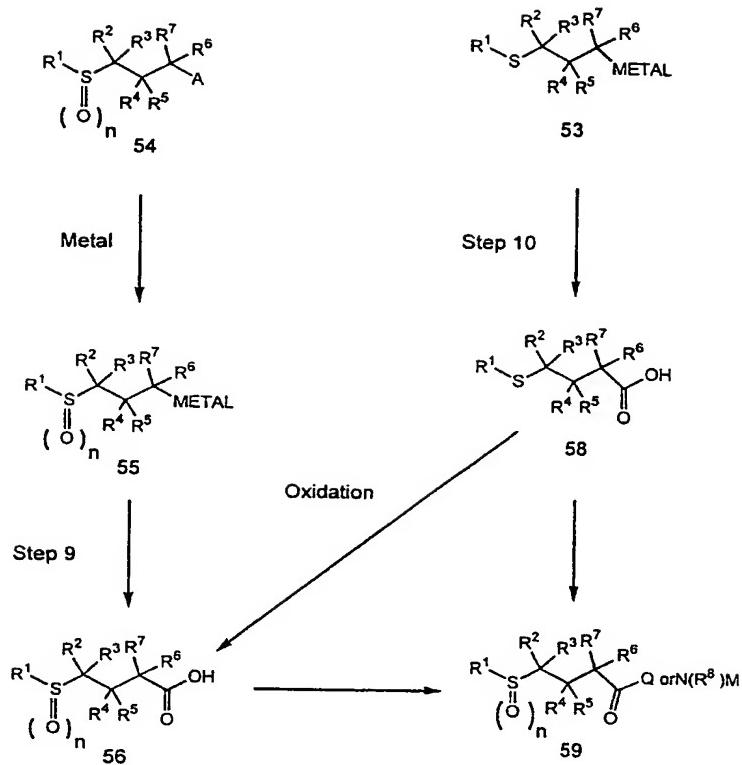
Where A is Cl, Br, I, Tosylate (Ts), Mesylate (Ms), Triflate and the like.

- 83 -

SCHEME B



- 84 -

SCHEME B
continued

$\text{A} = \text{Cl}, \text{Br}, \text{I}, \text{Tosylate}, \text{Mesylate}, \text{Triflate}$ and the like.

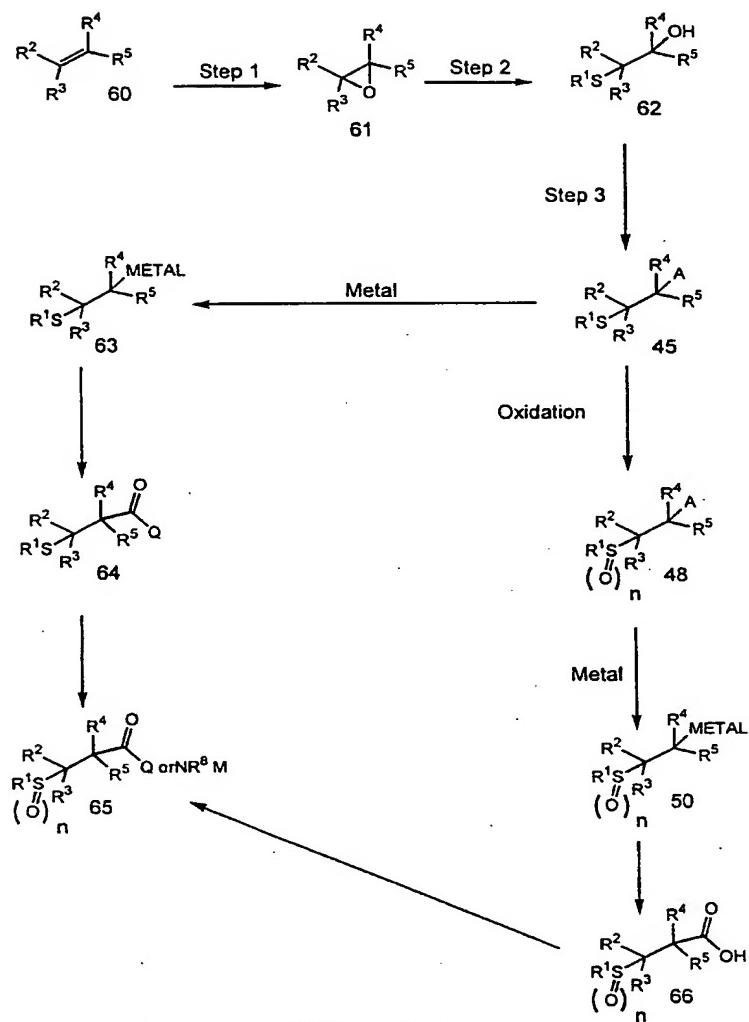
$n = 0, 1, 2$

$\text{Q} = \text{Alkoxy, Arylalkoxy, H, OH, Amino}$

$\text{M} = \text{H, Arylalkyl, Cycloalkoxyalkyl}$

- 85 -

SCHEME C



A = Cl, Br, I, Tosylate, Mesylate, Triflate and the like.

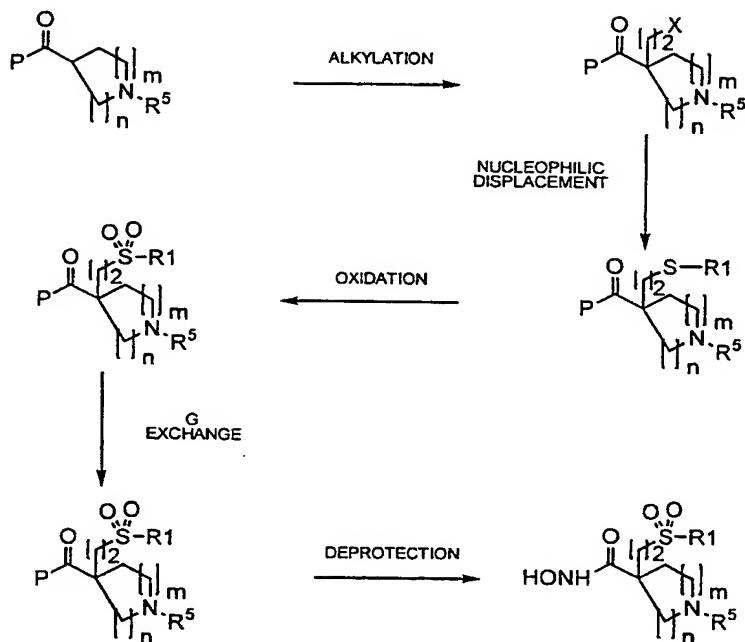
n = 0, 1, 2

Q = Alkoxy, Aryloxy, H, OH, Amino

M = H, Arylalkyl, Cycloalkoxyalkyl

- 86 -

SCHEME D



R^1 , R^5 , n AND m ARE AS DEFINED IN
FORMULA I; AND X IS A LEAVING GROUP

The above syntheses, as with all of the
5 reactions discussed herein, can be carried out under
a dry inert atmosphere such as nitrogen or argon if
desired. Selected reactions known to those skilled
in the art, can be carried out under a dry atmosphere
such as dry air whereas other synthetic steps, for
10 example, aqueous acid or base ester or amide
hydrolyses, can be carried out under laboratory air.

The compounds of this invention are
described above. This description includes 4-
sulfonehydroxamates and hydroxamate derivatives as
15 defined wherein 4 refers to the position of the

-87-

sulfonyl group removed from the carbonyl group of the hydroxamic acid group. The placement of that sulfur can also be shown by using the terms alpha (), beta (), gamma () or omega () wherein alpha is the 2-
5 position relative to the carboxyl or carboxyl derivative carbonyl, beta is the 3- position relative to the carboxyl or carboxyl derivative carbonyl, gamma is the 4- position relative to the carboxyl or carboxyl derivative carbonyl and omega is the last
10 position relative to the carboxyl or carboxyl derivative. Omega is a general term that denotes the last position in a chain without regard to the length of the chain.

As non-limiting examples, oxidations,
15 reductions, organometallic additions, hydrolyses, SN₂ reactions, conjugate additions, carbonyl additions, aromatic displacements and the like can be included. A person skilled in the art can apply the reactions to these compounds or readily adapt or change
20 synthetic procedures to a specific example as required.

In general, the choices of starting material and reaction conditions can vary as is well known to those skilled in the art. Usually, no single
25 set of conditions is limiting because variations can be applied as required and selected by one skilled in the art. Conditions can also be selected as desired to suit a specific purpose such as small scale preparations or large scale preparations. In either
30 case, the use of less safe or less environmentally sound materials or reagents is usually be minimized. Examples of such less desirable materials are

- 88 -

diazomethane, diethyl ether, heavy metal salts, dimethyl sulfide, chloroform, benzene and the like.

Various reactions illustrated in the above Schemes can be base mediated by the use of catalytic amounts of some bases or carried out with an equivalent or more of a base by the addition of an additional reagent or the thiol reagent can be a preformed thiol salt such as the sodium salt of a thiophenol. Bases that can be used include, for example, metal hydroxides such as sodium, potassium, lithium or magnesium hydroxide, oxides such as those of sodium, potassium, lithium, calcium or magnesium, metal carbonates such as those of sodium, potassium, lithium, calcium or magnesium, metal bicarbonates such as sodium bicarbonate or potassium bicarbonate, primary (I°), secondary (II°) or tertiary (III°) organic amines such as alkyl amines, arylalkyl amines, alkylarylalkyl amines, heterocyclic amines or heteroaryl amines, ammonium hydroxides or quaternary ammonium hydroxides.

As non-limiting examples, such amines can include triethyl amine, trimethyl amine, diisopropyl amine, methyldiisopropyl amine, diazabicyclononane, tribenzyl amine, dimethylbenzyl amine, morpholine, N-methylmorpholine, N,N'-dimethylpiperazine, N-ethylpiperidine, 1,1,5,5-tetramethylpiperidine, dimethylaminopyridine, pyridine, quinoline, tetramethylethylenediamine and the like. Non-limiting examples of ammonium hydroxides, usually made from amines and water, can include ammonium hydroxide, triethyl ammonium hydroxide, trimethyl ammonium hydroxide, methyldiisopropyl ammonium hydroxide, tribenzyl ammonium hydroxide,

- 89 -

dimethylbenzyl ammonium hydroxide, morpholinium hydroxide, N-methylmorpholinium hydroxide, N,N'-dimethylpiperazinium hydroxide, N-ethylpiperidinium hydroxide, and the like. As non-limiting examples, 5 quaternary ammonium hydroxides can include tetraethyl ammonium hydroxide, tetramethyl ammonium hydroxide, dimethyldiisopropyl ammonium hydroxide, benzylmethyldiisopropyl ammonium hydroxide, methyldiazabicyclononyl ammonium hydroxide, 10 methyltribenzyl ammonium hydroxide, N,N-dimethylmorpholinium hydroxide, N,N,N', N',-tetramethylpiperazinium hydroxide, and N-ethyl-N'-hexylpiperidinium hydroxide and the like.

Metal hydrides, amide or alcoholates such 15 as calcium hydride, sodium hydride, potassium hydride, lithium hydride, sodium methoxide, potassium tert-butoxide, calcium ethoxide, magnesium ethoxide, sodium amide, potassium diisopropyl amide and the like may also be suitable reagents. Organometallic 20 deprotonating agents such as alkyl or aryl lithium reagents such as methyl, phenyl or butyl lithium, Grignard reagents such as methylmagnesium bromide or methymagnesium chloride, organocadmium reagents such as dimethylcadmium and the like can also serve as 25 bases for causing salt formation or catalyzing the reaction. Quaternary ammonium hydroxides or mixed salts are also useful for aiding phase transfer couplings or serving as phase transfer reagents.

The reaction media can comprise a single 30 solvent, mixed solvents of the same or different classes or serve as a reagent in a single or mixed solvent system. The solvents can be protic, non-protic or dipolar aprotic. Non-limiting examples

-90-

of protic solvents include water, methanol (MeOH), denatured or pure 95% or absolute ethanol, isopropanol and the like. Typical non-protic solvents include acetone, tetrahydrofuran (THF), 5 dioxane, diethylether, tert-butylmethyl ether (TBME), aromatics such as xylene, toluene, or benzene, ethyl acetate, methyl acetate, butyl acetate, trichloroethane, methylene chloride, ethylenedichloride (EDC), hexane, heptane, isooctane, 10 cyclohexane and the like. Dipolar aprotic solvents include compounds such as dimethylformamide (DMF), dimethylacetamide (DMAc), acetonitrile, nitromethane, tetramethylurea, N-methylpyrrolidone and the like.

Non-limiting examples of reagents that can 15 be used as solvents or as part of a mixed solvent system include organic or inorganic mono- or multi-protic acids or bases such as hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, formic acid, citric acid, succinic acid, triethylamine, 20 morpholine, N-methylmorpholine, piperidine, pyrazine, piperazine, pyridine, potassium hydroxide, sodium hydroxide, alcohols or amines for making esters or amides or thiols for making the products of this invention and the like. Room temperature or less or 25 moderate warming (-10°C to 60°C) are the preferred temperatures of the reaction. If desired, the reaction temperature might be about -76°C to the reflux point of the reaction solvent or solvents.

An intermediate thioether can be oxidized 30 to the sulfone in one step using two equivalents to oxidizing agent. Reagents for this process can, in a non-limiting example, include peroxymonosulfate (OXONE®), hydrogen peroxide, meta-chloroperbenzoic

-91-

acid, perbenzoic acid, peracetic acid, perlactic acid, tert-butyl peroxide, tert-butyl hydroperoxide, tert-butyl hypochlorite, sodium hypochlorite, hypochlorous acid, sodium meta-periodate, periodic acid and the like. Protic, non-protic, dipolar aprotic solvents, either pure or mixed, can be chosen, for example, methanol/water.

The oxidation can be carried out at temperature of about -78° to about 50° degrees 10 centigrade and normally selected from a range -10°C to about 40°C. Preparation of a desired sulfone can be carried out in a two-step process using about one equivalent of oxidizing agent to first form the sulfoxide at about 0°C. A second oxidation then 15 produces the sulfone.

The solvents listed above can be used with these selective oxidations with, for example, methanol or methanol/water being preferred along with a temperature of from about -10°C to 30°C. It can be 20 desirable in the case of more active oxidizing agents, but not required, that the reactions be carried out under an inert gas atmosphere with or without degassed solvents.

A hydroxamate can be prepared from the 25 corresponding ester by reaction of the ester with one or more equivalents of hydroxylamine hydrochloride at room temperature or above in a solvent or solvents such as those listed above. This exchange process can be further catalyzed by the addition of 30 additional acid.

Alternatively, a base such as a salt of an alcohol used as a solvent, for example, sodium methoxide in methanol, can be used to form

-92-

hydroxylamine in situ which can exchange with an ester or amide. The exchange can be carried out with a protected hydroxyl amine such as tetrahydropyranylhydroxyamine (THPONH₂),

- 5 benzylhydroxylamine (BnONH₂), and the like in which case compounds in which the ester is a tetrahydropyranyl (THP) or benzyl (Bn) ester.

Removal of the protecting groups when desired, for example, following further

- 10 transformations in another part of the molecule or following storage, is accomplished by standard methods well known in the art such as acid hydrolysis of the THP group or reductive removal of the benzyl group with hydrogen and a metal catalyst such as
- 15 palladium, platinum, palladium on carbon or nickel.

Oxidizable functional groups are readily recognized by those skilled in the art and alternative synthesis can be used such as the protection/deprotection sequence.

- 20 Acids can be converted into activated carbonyl compounds using reagents well known in the art including the peptide and protein synthesis and amino acid coupling or conjugation art. Examples of such reagents are thionyl chloride, oxalyl chloride,
- 25 phosphorus oxychloride, HOBT, isobutylchloroformate and the like. These valuable activated carbonyl intermediates can then be transformed into hydroxamic acids or hydroxamic acid derivatives such as H, benzyl or THP. Preparation of or interconversion
- 30 between the hydroxylamine or hydroxylamine derivative compounds or acids or amides or esters can be carried out by one skilled in the art using the methods discussed above or by other techniques.

-93-

The amine function in the intermediate compounds use a protecting group to facilitate the transformations. Decisions involving the selection of protecting groups and their use can be made by a 5 person skilled in the art. Especially useful are the techniques and reagents used in protein, peptide and amino acid coupling and transformation chemistry. The use of the tert-butoxycarbonyl (BOC), benzyloxycarbonyl (Z) and N,N-dibenzyl groups as will 10 15 as their synthesis and removal are examples of such protection schemes.

Coupling of the amino acids, amino esters, amino acid hydroxamates or hydroxamate derivatives and amino acid amides of the precursor (intermediate) 15 compounds with, for example, other amino acids, amines, alcohols, amides or acids is also carried out by methods well known in the art such as, for example, active ester or mixed anhydride couplings with preferred bases if required being moderate 20 tertiary amines such as N-methylmorpholine. Removal of a preexisting group that can also serve as a protecting group or blocking group such as the acetyl group and the like is also accomplished using standard hydrolysis conditions such as base 25 hydrolysis or exchange or acid exchange or hydrolysis.

In the case of compounds with an amine group, it is sometimes desirable to use acidic conditions with a reagent such as hydrogen peroxide 30 and/or in combination with an acidic reagent such as periodic acid, peracetic acid and the like. It should also be noted by one skilled in the art that hydrolysis or exchange of the acetyl group may or may

-94-

not effect hydrolysis or exchange of a ester, amide or hydroxamate function.

Preparation of yet another class of compounds of this invention, those containing the alpha-hydroxy carbonyl function, typically uses the SN₂ class of reactions. A bimolecular nucleophilic displacement (SN₂) reaction is illustrated in a step wherein a halogen is displaced by a thiol compound or the salt of a thiol compound. The thiol anion can be derived from a preformed salt or the salt can be formed in situ via addition of a base.

Preferred bases are those that are hindered such that competition with thiolate anion in a two stage reaction is minimized. The solvents, solvent mixtures or solvent/reagent mixtures discussed are satisfactory but non-protic or dipolar aprotic solvents such as acetone, acetonitrile, DMF and the like are examples of a preferred class.

A protecting group P on the alpha-hydroxy group can also be utilized. Such protecting groups can include acyl groups, carbamoyl groups, ethers, alkoxyalkyl ethers, cycloalkyloxy ethers, arylalkyl groups trisubstituted silyl groups and the like. Examples of such protecting groups include acetyl, THP, Benzyl, Z, tert-butyldimethylsilyl (TBDMS) groups. The preparation of such protected alcohols as well as the removal of the protecting groups is well known in the art and its practitioners.

The selection of an atmosphere for the reactions of these Schemes as well as the other Schemes depends, as usual, a number of variables known to those skilled in the art. The choices can be an inert atmosphere such as nitrogen, argon,

-95-

helium and the like or normal or dry air. Preferred is the use of an inert atmosphere if there is an uncertainty as to the requirements of the process.

One of these variables particularly
5 requiring the attention of the skilled person is control of oxidation by air or another means of a thiol or the salt of a thiol to its corresponding disulfide or mixed disulfide. The used of a damp atmosphere while carrying out an organometallic
10 compound requiring synthesis not desirable for either economic or safety reasons whereas the use of air is normal for aqueous hydrolysis or exchange reactions where oxidation, for example, is not probable.

Addition of an organometallic reagent such
15 as a Grignard Reagent, lithium organometallic reagent, zinc organometallic reagent, cadmium organometallic reagent, sodium organometallic reagent or potassium organometallic reagent to a carbonyl group such as an aldehyde, ketone, ester, amide
20 (primaryI, secondary, tertiary), acid chloride, anhydride, mixed anhydride, hydroxamate derivative (mono- or bis-), carbonate, carbamate or carbon dioxide is illustrated in the Schemes such as Schemes A, B and C. The products of such reactions of
25 organometallic compounds with carbonyl compounds are well known to those skilled in the art. Well know examples include the preparation of alcohols by reaction with aldehydes, acids by reaction with carbon dioxide and esters by reaction with carbonate
30 esters.

For example, in Scheme A, the product of such a reaction can be an alcohol such as compound 39 or an ester, amide, ketone or aldehyde. It is

- 96 -

also recognized by those skilled in the art that the carbonyl compound and the organometallic compound can be exchanged or interchanged or otherwise manipulated to synthesize the same or a similar compound. For 5 example, although not contemplated herein, carbonyl compound 38 in Scheme A wherein R⁶ is methyl (or ethyl) can be reacted with ethyl magnesium bromide (or methyl magnesium bromide) to form compound 39 where R⁷ is ethyl (or methyl) and organometallic 10 compound 53 in Scheme B where one of R⁷ and R⁶ is methyl one is ethyl can be treated with water to also form compound 39.

An alcohol can also be converted into a halogen or sulfonate ester. Either product, as shown 15 with the sulfides, can be oxidized or, once oxidized, reduced back to a sulfide or sulfoxide. In addition, the alcohol with the sulfur oxidized can also be converted into, for example, its corresponding halogen or sulfonated ester.

20 The halogen compounds such as those in Schemes A, B and C, for example, with or without the sulfur oxidized can be reacted with a metal to form an organometallic reagent such as those listed above. The organometallic compound can then be reacted with 25 a carbon-oxygen double bond-containing molecule to produce precursors to compounds of this invention including homologous acids, esters, amides (primary, secondary, tertiary), ketones, aldehydes and the like.

30 If the product of the reaction of an organometallic compound with a carbonyl compound is itself another carbonyl containing compound such as shown, for example, by the synthesis of compounds 64

-97-

or 65 in Scheme C, the product can be either a metalloprotease inhibiting product of this invention or an intermediate for the synthesis of a homologous metalloprotease inhibiting compound of this 5 invention. As was discussed above with respect to alcohols and illustrated in these Schemes, these carbonyl products can be oxidized at sulfur before or after further modification.

A lactone ring where R² through R⁷ 10 inclusive are as defined above can be opened with a thiolate anion to provide a 4-thia acid (omega-thia acid, gamma-thia acid) or salt. An example of a preferred thiol is 4-phenoxybenzenethiol. The sulfide formed can then be oxidized to the 15 corresponding sulfone, converted to the hydroxamate or protected hydroxamate, deprotected if required all by methods discussed and illustrated above and known in the art.

Alternatively, a Lewis acid in the presence 20 of a thiol can be used to form the thia acid. Opening of the lactone with a Lewis such as zinc bromide or zinc chloride in the presence of thionyl bromide or thionyl chloride can provide an omega-halo acid halide (activated carbonyl). This intermediate 25 derivatives as desired at the carbonyl carbon can be prepared to provide a protected carbonyl compounds such as an ester or an amide or used to form a hydroxamic acid or protected hydroxamic acid directly; i.e., a omega-halo ester, amide, hydroxamic 30 acid or protected hydroxamate.

The 4-chloro or 4-bromo group can be displaced via a nucleophilic substitution reaction (SN₂) using a -SR¹ reagent to provide a thia-compound

-98-

that can then be oxidized as outlined above to provide a desired compound. Preferred lactones can include 2-methylbutyrolactone, 2-hydroxy-3,3-dimethylbutyrolactone and 2-piperidylbutyrolactone.

5 Preferred omega-haloesters include, methyl 2,2-dimehyl-4 chlorobutyrate and ethyl 4-bromobutyrate.

Alpha-halolactones can be utilized in the preparation of compounds of this invention wherein the alpha-carbon of the product hydroxamic acids are 10 substituted with a nucleophile such as a hydroxyl, ether, azide or an amine. These intermediates, when stable to the reaction conditions, properly protected or converted in a later step to the desired function can provide substrates for the lactone dependant 15 reactions discussed above. Bromobutyrolactone is a preferred halolactone.

Compounds of this invention can be prepared by alkylation of a carbanion (nucleophile) generated from a protected carboxylic acid using processes 20 known in the art. Protecting groups for the carboxyl function include, for example, esters such as tert-butyl esters. Bases for forming the anion are can be organometallic reagents such as tert-butyl lithium, metal amides such as lithium diisopopyl amide (LDA) 25 or alkoxides such as potassium tert-butoxide. Other candidate bases are discussed above.

Following or during formation of the anion, the alkylating agent (electrophile) is added which undergoes a nucleophilic substitution reaction.
30 Electrophilic substrates for displacement can include, for example, dihalo alkanes such as 1,2-dihaloalkanes or mono-halo-mono sulfated alkanes or bisulfonate alkane esters. 1,2-di-Bromoethanes, 1-

-99-

chloro-2, bromoethanes, 1-chloro-2-tosylethanes and 1,2-di-toluenesulfonylethanes are examples of such bis-electrophiles. 1-Bromo-2-chloro-ethane is a preferred electrophile.

- 5 Activated ester groups are well known in the art and can include, for example, di-esters such as malonates, ester-ketones such as acetoacetic esters or ester-aldehydes that are subject to carbonyl addition reactions. Alkylation with one
10 equivalent of alkylating agent followed by derivatization of the new omega carbonyl group with, for example, an organometallic reagent or reduction to form an alcohol which can then be derivatized to form a carbon halogen bonds or an activated ester
15 such as a sulfate ester. These omega-substituted compounds can serve as substrates for the thioate displacement and oxidation reactions discussed above to form the carboxylic acid compounds or intermediates of this invention.
- 20 Omega-haloalcohols can be useful starting materials for the preparation of compounds of this invention using alternative synthetic sequences from those discussed above. They can serve as substrates for R¹ thiolate displacement (S_N2) to provide 4-sulfides (thio ethers) which can then be oxidized to the desired sulfones. The HS-R¹ compounds can be prepared as discussed below and oxidized as discussed above. Preparation of the R¹ group can be via an intermediate such as a fluorothiophenol followed by
25 displacement of the fluoride with a second nucleophile to produce compounds or intermediates of this invention. Flourothiophenol and phenol and 2,3-dimethyl phenol are examples of preferred thiols and
30

-100-

phenols, respectively. The sulfone alcohols can be oxidized to the corresponding carboxylic acids as well as to the corresponding aldehydes.

- The carboxylic acids or protected
- 5 carboxylic acids can be utilized as presented herein. The aldehydes can serve as useful intermediates for homologation to an alpha-hydroxysulfone acid compound that can serve as a substrate for preparation of a hydroxamic acid or hydroxamate of this invention.
- 10 Homologation of an aldehyde can be carried out by adding a cyanide to the aldehyde to form a alpha-cyano-omegasulfone (cyanohydrin) which can then be hydrolysed with an acid such as those discussed above to form a alpha-hydroxy carboxylic acid useful in the
- 15 synthesis of compounds of this invention.
- Cyanohydrins can be prepared by methods well known in the art such as treatment of an aldehyde with a metal cyanide, hydrogen cyanide or trimethylsilylcyanide. Trimethylsilylcyanide is a preferred reagent.
- 20 The preparation of compounds of this invention based on alpha-oxygen-substituted compounds such as the hydroxyl group is discussed and illustrated and the methods are well known in the art. Protection of the alcohols of this invention or
- 25 of the intermediate alcohols used in this invention is also well known.

- The preparation of ethers can be carried out by forming a salt of the alcohol and treating this nucleophile with an electrophile such as a halide or an activated ester such as a sulfate ester.
- 30 The salt is formed by treating the alcohol with a base such as is discussed above. Examples of such

-101-

bases are lithium alkyls, metal hydrides or the metal salts of an amine such as LDA.

Halides can be chlorides, bromides or iodides and sulfates can be, for example, benzene 5 sulfonates, tosylates, mesylates or triflates. An example of a preferred electrophile is 2-chloromethylpyridine and a preferred base is sodium hydride. Alternatively, the alcohol can be converted into a leaving group (electrophilic reagent) and then 10 treated with a nucleophile. Examples of such leaving groups include sulfate esters such tosylates, mesylates and triflates whose preparation is discussed above. The triflate is a preferred leaving group.

15 Displacement of these groups with nucleophiles is well known in the art and discussed and/or illustrated above. The nucleophiles can be hydroxide to allow inversion of stereochemistry, alkoxides to form ethers, amines or ammonia to form 20 substituted amines or an azide anion to form an azide. A preferred nucleophile the is tetra-(n-butyl)ammonium azide. The azido compound, for example, can be reduced to form the amino acid. Reductions are discussed above and are well known in 25 the art. A preferred method is hydrogenation with palladium on carbon catalyst.

The amines, including the amino acids, of this invention can be acylated or alkylated by methods well known in the art. The amides formed can 30 be considered as protected amines or as end products of this invention. Acylation to form such derivatives as tert-butoxycarbonyl and carbobenzyloxy carbonyl group is discussed above. Other acyl (Ac)

-102-

groups can be, for example, acetyl, haloacetyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl or other groups as required. The amines can be acylated using anhydrides, mixed anhydrides, 5 acid chlorides or activated esters. Usually such acylations are carried out in presence of a base such as the bases discussed above and well known in the art. Examples are N-methyl-morpholine, triethylamine and the like.

10 The carboxyl compounds useful herein having amide substituents can be treated, converted or interconverted as shown and/or discussed above to form the products of this invention. In addition, the haloacetyl compounds such as the preferred 2- 15 chloroacetamide derivative can be treated with an amine as a nucleophile to yield an aminoacid. Again, these reactions are well known in the art. A preferred amine is morpholine.

The cyclic amino acids used to prepare 20 desired compounds can be prepared in ways known to those skilled in the art. Reduction of heteroaryl or unsaturated or partially unsaturated heterocycles can be carried out. For example, the six membered ring compounds can be synthesized by reduction of the 25 corresponding 2-, 3- or 4- pyridine carboxylic acids, 2-, or 3-pyrazole carboxylic acids or derivatives thereof. The reduction can be hydrogenation in the presence of a catalyst or hydride reduction using a hydride transfer agent such as lithium aluminum 30 hydride. The starting amino acids or their derivatives, such as ethyl isonipecotate, ethyl nipecotate, pipecolinic acid, proline or its isomers, pyroglutamate or its isomers are starting materials

-103-

that can be used to prepared a compound of this invention.

The R, S and RS isomers of the amino acids can be used. Some starting material can be obtained 5 from commercial sources. A preferred starting material is ethyl isonipecotate.

Alkylation of the aminoacid at the carbon alpha to the carbonyl group to form a useful compound can be carried out by first forming an anion using a 10 base. Exemplary bases are discussed elsewhere. The preferred bases are strong bases that are either hindered and/or non-nucleophilic such as lithium amides, metal hydrides or lithium alkyls. A preferred base is lithium diisopropylamide (LDA) in a 15 dipolar aprotic solvent or THF.

Following or during formation of the anion, an alkylating agent (an electrophile) is added which undergoes a nucleophilic substitution reaction. Non-limiting examples of such alkylating agents are 1,2- 20 dihaloalkanes or haloalkanes also substituted by an activated ester group. Activated ester groups are well known in the art and can include, for example, an ester of a 2-halo-alcohol such as a bromo-, iodo- or chloro-ethane para-toluene sulfonate, triflate or 25 mesylate. A preferred alkylating agents is 1-bromo-2-chloroethane.

The nitrogen substituent on the cyclic aminoacid portion of the compounds of this invention can be varied. In addition, this can be accomplished 30 at different stages in the synthetic sequence based on the needs and objectives of the skilled person preparing the compounds of this invention.

-104-

The N-side chain variations can include replacing the hydrogen substituent with a alkyl, arylalkyl, alkene or alkyne. This can be accomplished by methods well known in the art such as 5 alkylation of the amine with an electrophile such as halo- or sulfate ester (activated ester) derivative of the desired sidechain. This can be done in the presence of a base such as those discussed above and in a pure or mixed solvent as discussed above. A 10 preferred base is postassium carbonate and a preferred solvent is DMF.

The alkenes and alkynes can be reduced. if desired, by, for example, hydrogenation with a metal catalyst and hydrogen, to an alkyl or arylalkyl 15 compound of this invention and the alkyne or arylalkyne can be reduced to a alkene or alkane with under catalytic hydrogenation conditions as discussed above dor with an deactivated metal catalyst. Catalysts can include, for example, Pd, Pd on Carbon, 20 Pt, PtO₂ and the like. Less robust catalysts include such thing as Pd on BaCO₃ or Pd with quinoline or/and sulfur.

An alternative method for alkylation of the amine nitrogen is reductive alkylation. This 25 process, well known in the art, allows treatment of the secondary amine with an aldehyde or ketone in the presence of a reducing agent such as borane, borane:THF, borane:pyridine, lithium aluminum hydride. Alternatively, reductive alkylation can be 30 carried out hydrogenation conditions in the presence of a metal catalyst. Catalysts, hydrogen pressures and temperatures are discussed above and are well

-105-

known in the art. A preferred reductive alkylation catalyst is borane:pyridine complex.

The compounds of this invention include compounds wherein the substituent on nitrogen of the 5 cyclic amino acids as listed above provide amino acid carbamates. Non-limiting examples of these carbamates are the carbobenzoxycarbonyl (Z, CBZ, benzyloxycarbonyl), isobutyloxycarbonyl and tert-butoxycarbonyl (BOC, t-BOC) compounds. These 10 materials can be made, as discussed above, at various stages in the synthesis based on the needs and decisions made by a person skilled in the art using methods well known in the art.

Useful synthetic techniques and reagents 15 include those used in protein, peptide and amino acid synthesis, coupling and transformation chemistry. The use of the tert-butoxycarbonyl (BOC) and benzyloxycarbonyl (Z) as well as their synthesis and removal are examples of such protection or synthesis 20 schemes discussed above. Transformations of amino acids, amino esters, amino acid hydroxamates, amino acid hydroxamate derivatives and amino acid amides of this invention or compounds used in this invention can be carried out as discussed and/or illustrated 25 above. This includes, for example, active ester or mixed anhydride couplings wherein preferred bases, if required, are tertiary amines such as N-methylmorpholine.

Reagents for protection of the amine group 30 of the protected amino acids include carbobenzoxy chloride, iso-butylchloroformate, tert-butoxycarbonyl chloride, di-tert-butyl dicarbonate and the like which are reacted with the amine in non-protic or

-106-

dipolar aprotic solvents such as DMF or THF or mixtures of solvents. A preferred reagent is di-tert-butyl dicarbonate and a preferred solvent is THF. Further conversion of the cyclic amino acids of 5 this invention including alkylation, displacement with a thiol or thiolate, oxidation to a sulfone, and conversion into a hydroxamic acid or hydroxamate derivative can be carried out discussed herein.

Sulfone compounds such as those where R¹ is 10 nitroaryl can be prepared as compounds of this invention by synthesis of a thiol or thiolate nucleophile, displacement of an electrophile (X) by the nucleophilic thiol or thiolate and oxidation of the product thia ether (sulfide) to the sulfone. For 15 example, displacement of the electrophilic group X with a nitro-benzenethiol can yield a compound where R¹ is nitrobenzene that can be reduced to provide a useful amino compound wherein R¹ is an aniline. It should be noted that nitrobenzenethiol is an example 20 and not to be considered as limiting or required. Oxidation of the thioether product can be carried out as discussed below when desired.

The reduction of nitro groups to amines is will know in the art with a preferred method being 25 hydrogenation. There is usually a metal catalyst such as Rh, Pd, Pt, Ni or the like with or without an additional support such as carbon, barium carbonate and the like. Solvents can be protic or non-protic pure solvents or mixed solvents as required. The 30 reductions can be carried out at atmospheric pressure to a pressure of multiple atmospheres with atmospheric pressure to about 40 pounds per square inch (psi) preferred. The amino group can be

-107-

alkylated if desired, or acylated with, for example, an aroyl chloride, heteroaryl chloride or other amine carbonyl forming agent to form an R¹ amide.

The amino sulfone or thioether can also be
5 reacted with a carbonic acid ester chloride, a sulfonyl chloride, a carbamoyl chloride or an isocyanate to produce the corresponding carbamate, sulfonamides, or urea. Acylation of amines of this type are well known in the art and the reagents are
10 also well known.

Usually, these reactions are carried out in aprotic solvents under an inert or/and dry atmosphere at about 45°C to about -10°C. An equivalent of a non-competitive base is usually used with sulfonyl
15 chloride, acid chloride or carbonyl chloride reagents. Following or before this acylation step, synthesis of the hydroxamic acid products of this invention can proceed as discussed.

Other thiol reagents can also be used in
20 the preparation of compounds of this invention. Examples are fluoroaryl, fluoroheteroaryl, azidoaryl or azidoheteroaryl or heteroaryl thiol reagents. These thiols can be used a nucleophiles to as
discussed above. Oxidation to the corresponding
25 sulfone can then be carried out. The fluoro substituted sulfone can be treated with a nucleophile such as ammonia, a primary amine, a quaternary ammonium or metal azide salt, under pressure if desired, to provide an azido, amino or substituted
30 amino group that can then be reacted an activated benzoic or substituted benzoic acid derivative to form a benzamide. Azides can be reduced to an amino group using, for example, hydrogen with a metal

-108-

catalyst or metal chelate catalyst or by an activated hydride transfer reagent. Hydrazo compounds can be oxidized to azo compounds and axo compounds can be reduced to hydrazo compounds. The amines can be
5 acylated as discussed above.

Preferred methods of preparing aminethiol intermediates of this invention include protection of an aromatic or heteroaromatic thiol with trityl chloride to form the trityl thiol derivative,
10 treatment of the amine with as reagent such as an aromatic or heteraromatic acid chloride to form the amide, removal of the trityl group, with acid to form the thiol. Preferred acylating agents include benzoyl chloride and preferred trityl removing
15 reagents include trifluoroacetic acid and trisopropylsilane.

The fluorine on fluorosulfone intermediates can also be displaced with other aryl or heteroaryl nucleophiles to form compounds of this invention.
20 Examples of such nucleophiles include salts of phenols, thiophenols, -OH group containing aromatic heterocyclic compounds or -SH containing heteroaryl compounds.

Tautomers of such groups azo, hydrazo, -OH
25 or -SH are specifically included as useful isomers. A preferred method of preparing intermediates in the synthesis of the substituted sulfones is by oxidation of an appropriate acetophenone, prepared from a flouroacetophenone, with for example,
30 peroxymonosulfate, to form the corresponding phenol-ether. That phenol-ether is converted into its dimethylthiocarbamoyl derivative using dimethylthiocarbamoyl chloride, followed by

-109-

rearranging the dimethylthiocarbamoyl derivative with heat to provide the thiol required for preparation of the thioether intermediate.

Salts of the compounds or intermediates of 5 this invention are prepared in the normal fashion wherein acidic compounds are reacted with bases such as those discussed above to produce metal or nitrogen containing cation salts. Basic compounds such as amines can be treated with an acid to form the 10 amine salt. A preferred amine salt is the hydrochloride salt formed by reaction of the free base with HCl or hydrochloric acid.

Compounds of the present can possess one or more asymmetric carbon atoms and are thus capable of 15 existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes well known in the art, for example by 20 formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyl tartaric, dibenzoyl tartaric, ditoluoyl tartaric and camphorsulfonic acid and then separation of the 25 mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize 30 the separation of the enantiomers.

Still another available method involves synthesis of covalent diastereoisomeric molecules, e.g., esters, amides, acetals, ketals, and the like,

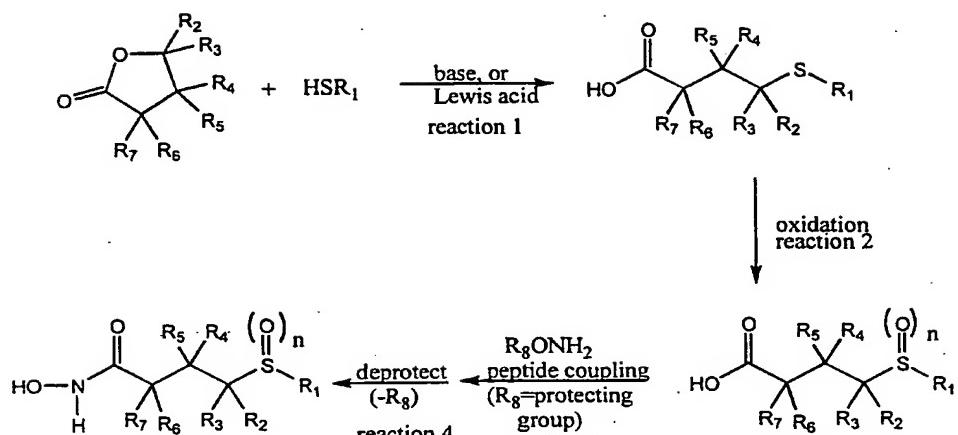
-110-

by reacting compounds of Formula I with an optically active acid in an activated form, a optically active diol or an optically active isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. In some cases hydrolysis to the parent optically active drug is not necessary prior to dosing the patient because the compound can behave as a prodrug. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials.

In addition to the optical isomers or potentially optical isomers discussed above, other types of isomers are specifically intended to be included in this discussion and in this invention. Examples include cis isomers, trans isomers, E isomers, Z isomers, syn- isomers, anti- isomers, tautomers and the like. Aryl, heterocyclo or heteroaryl tautomers, heteroatom isomers and ortho, meta or para substitution isomers are also included as isomers. Solvates or solvent addition compounds such as hydrates or alcoholates are also specifically included both as chemicals of this invention and in, for example, formulations or pharmaceutical compositions for delivery.

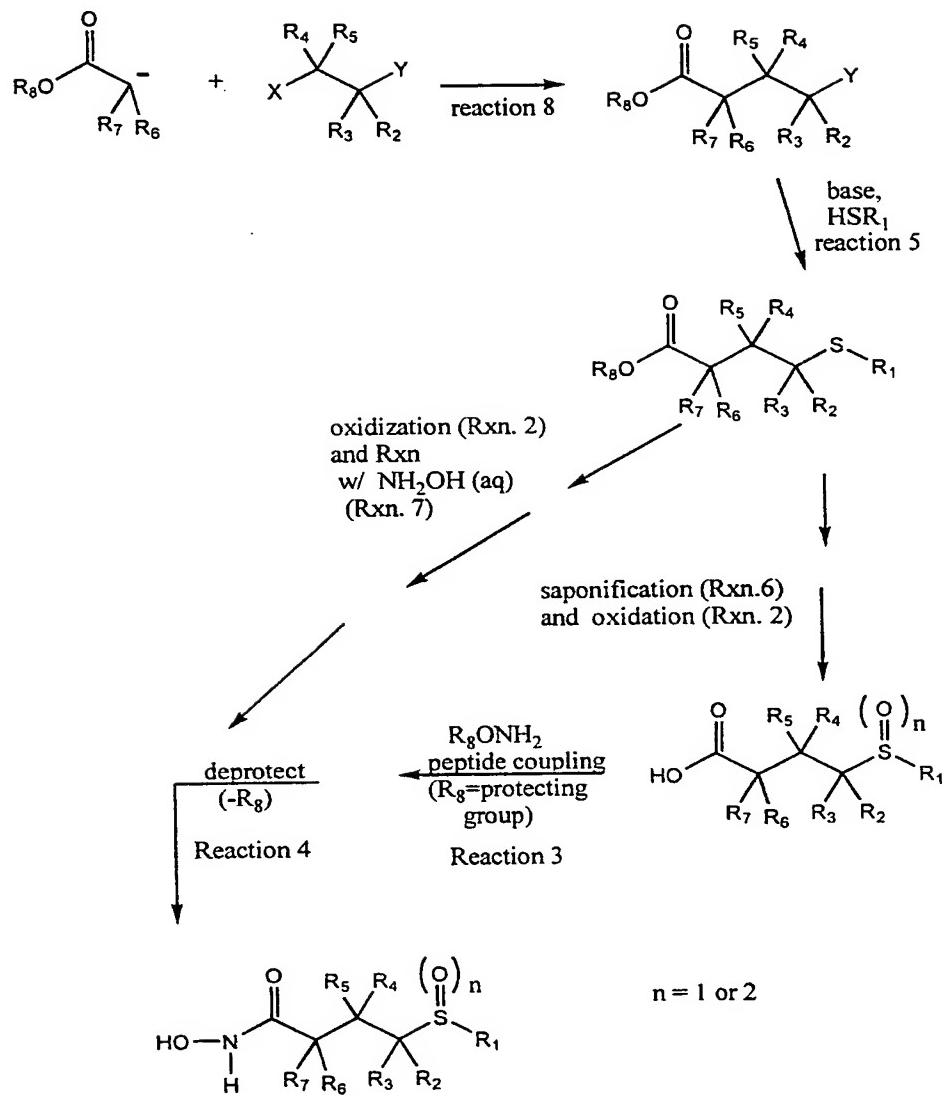
-111-

Scheme I



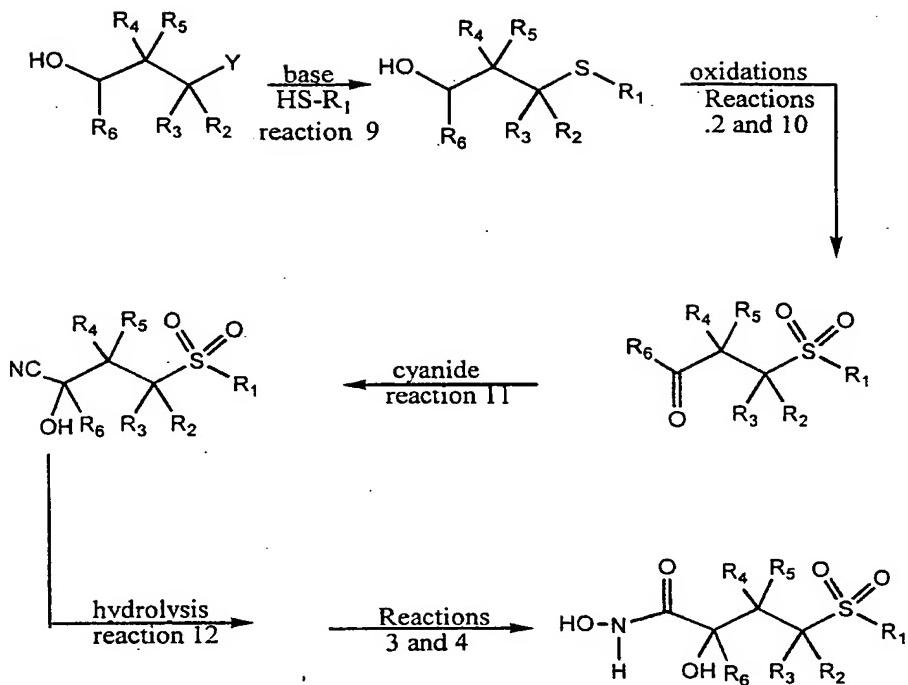
-112-

Scheme 2



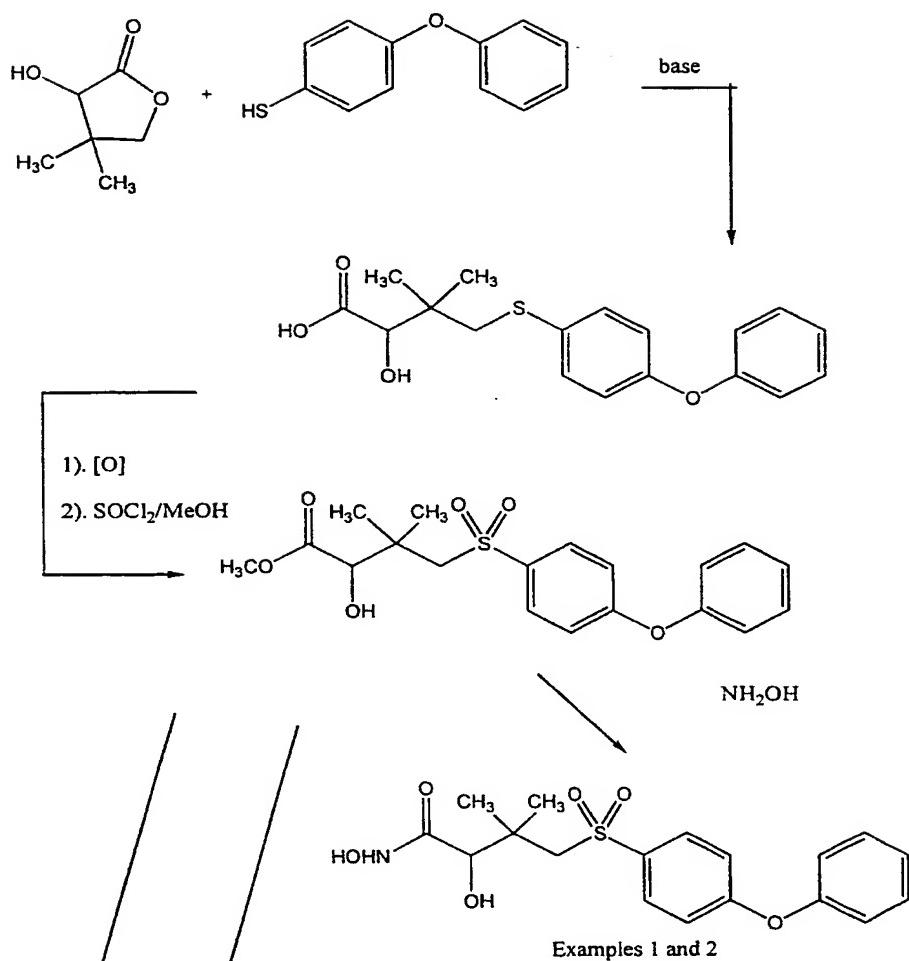
-113-

Scheme 3



-114-

Scheme 4A

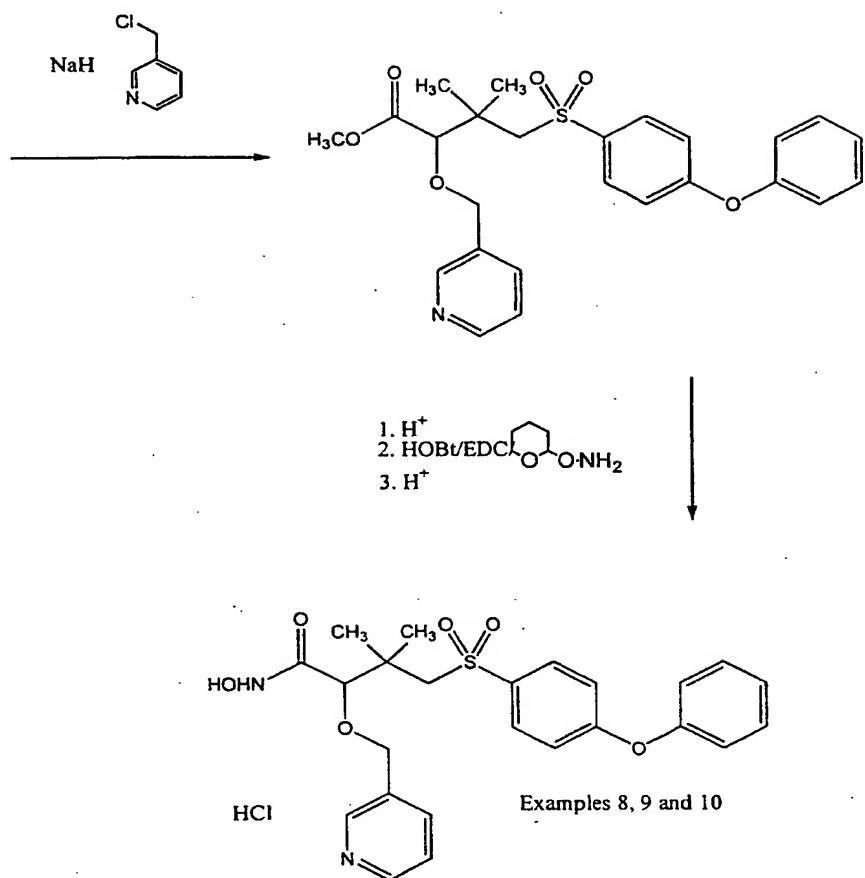


Scheme 4B

Scheme 4C

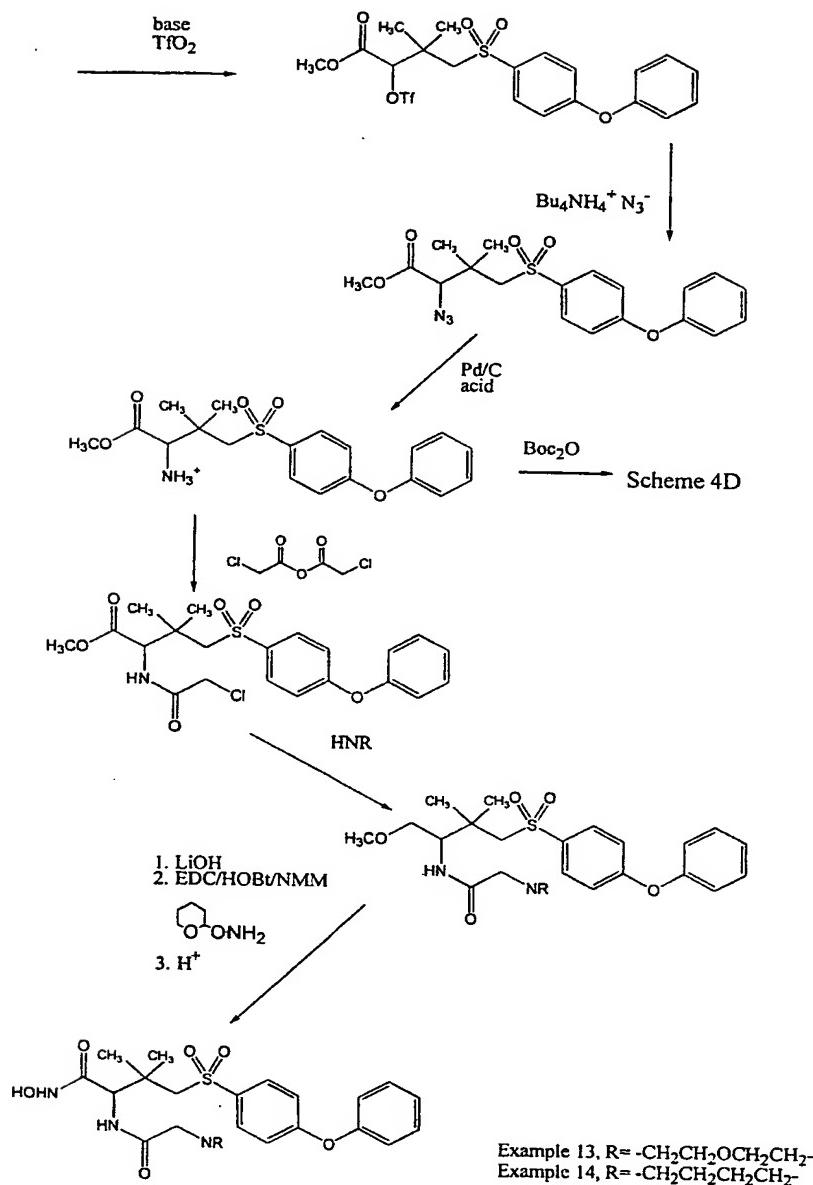
-115-

Scheme 4B



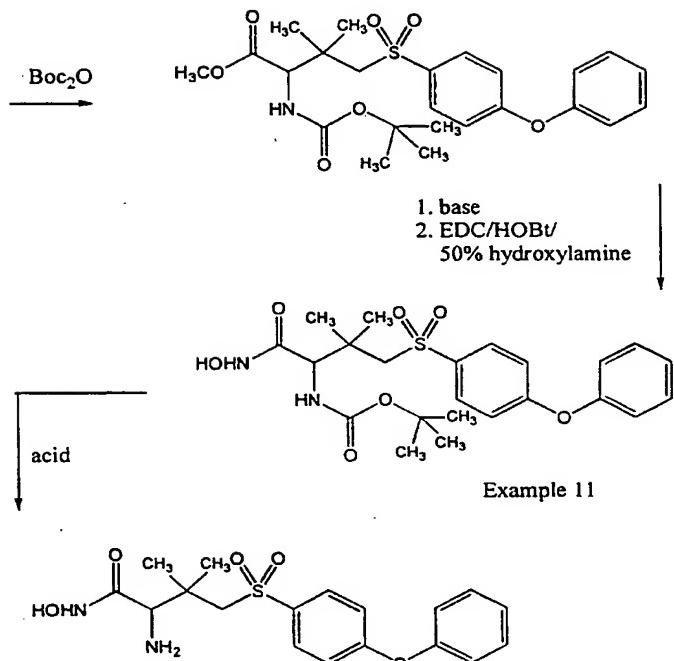
- 116 -

Scheme 4C



-117-

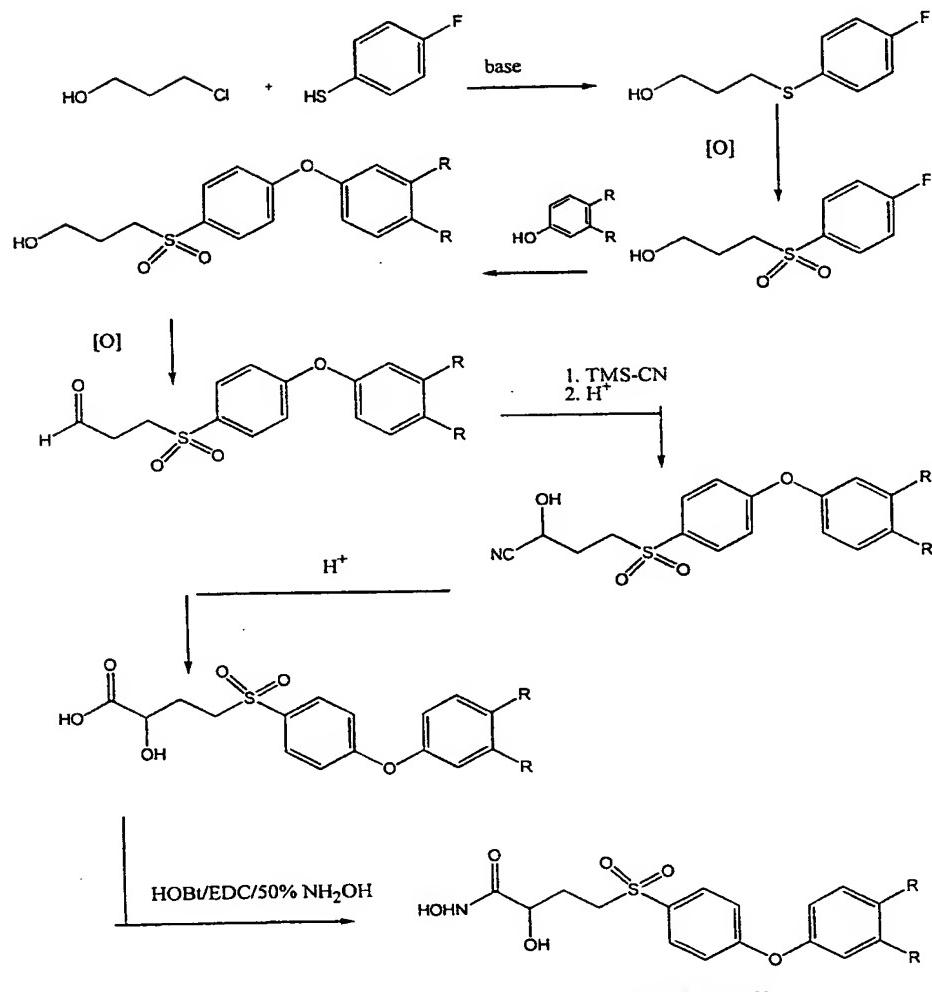
Scheme 4D



Example 12

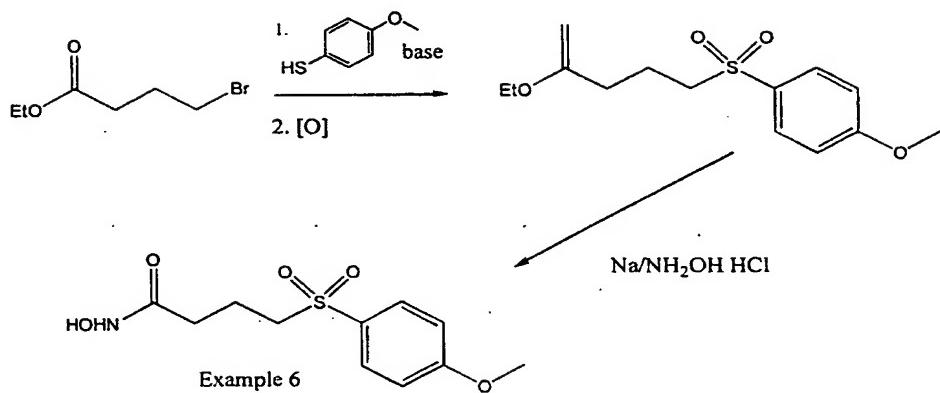
-118-

Scheme 5A

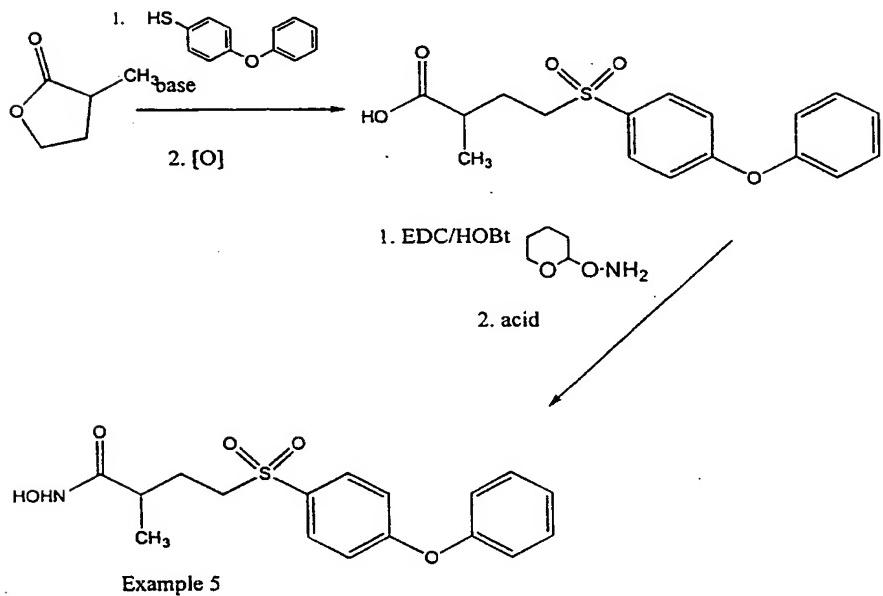


-119-

Scheme 5B

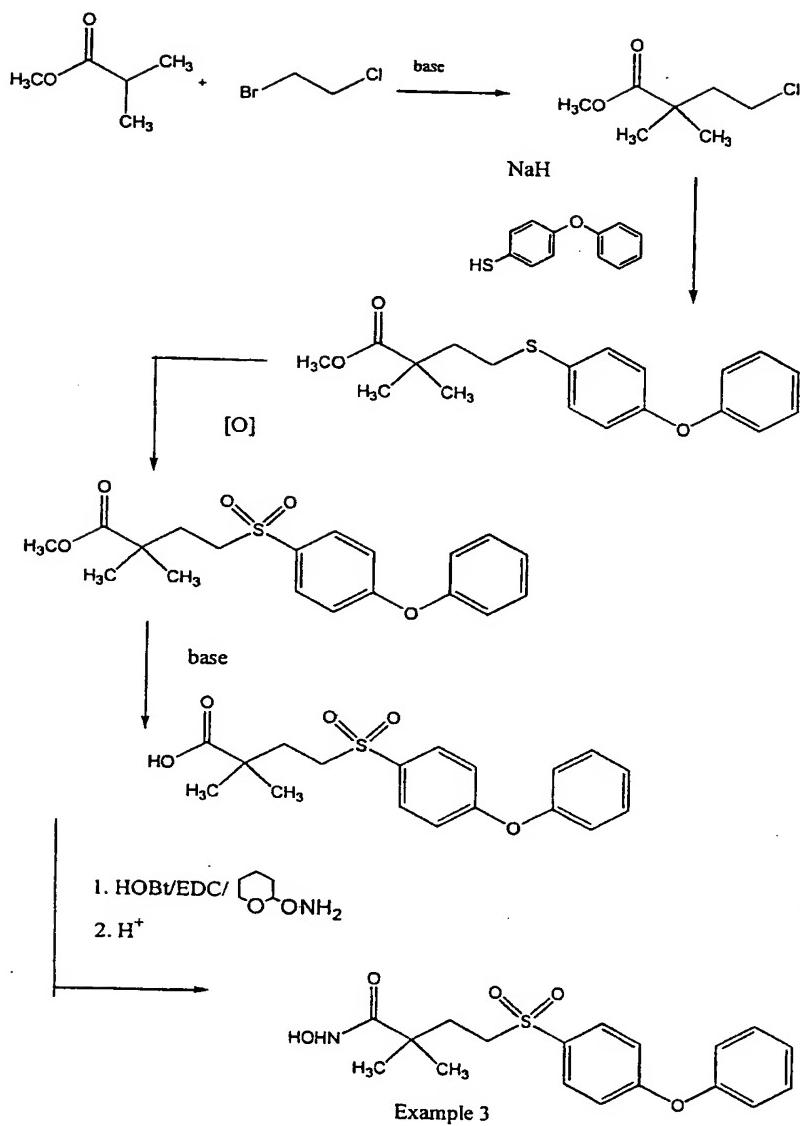


Scheme 5C



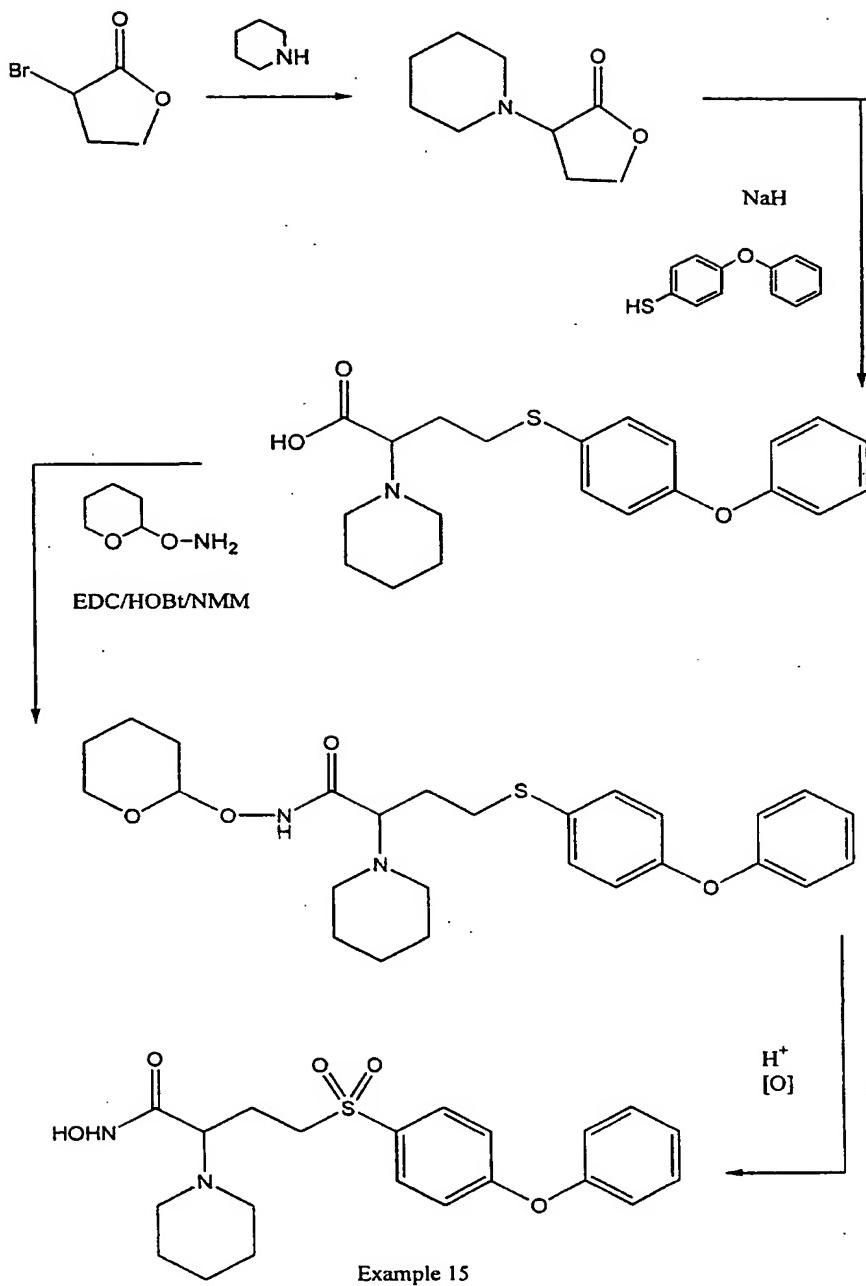
-120-

Scheme 6A



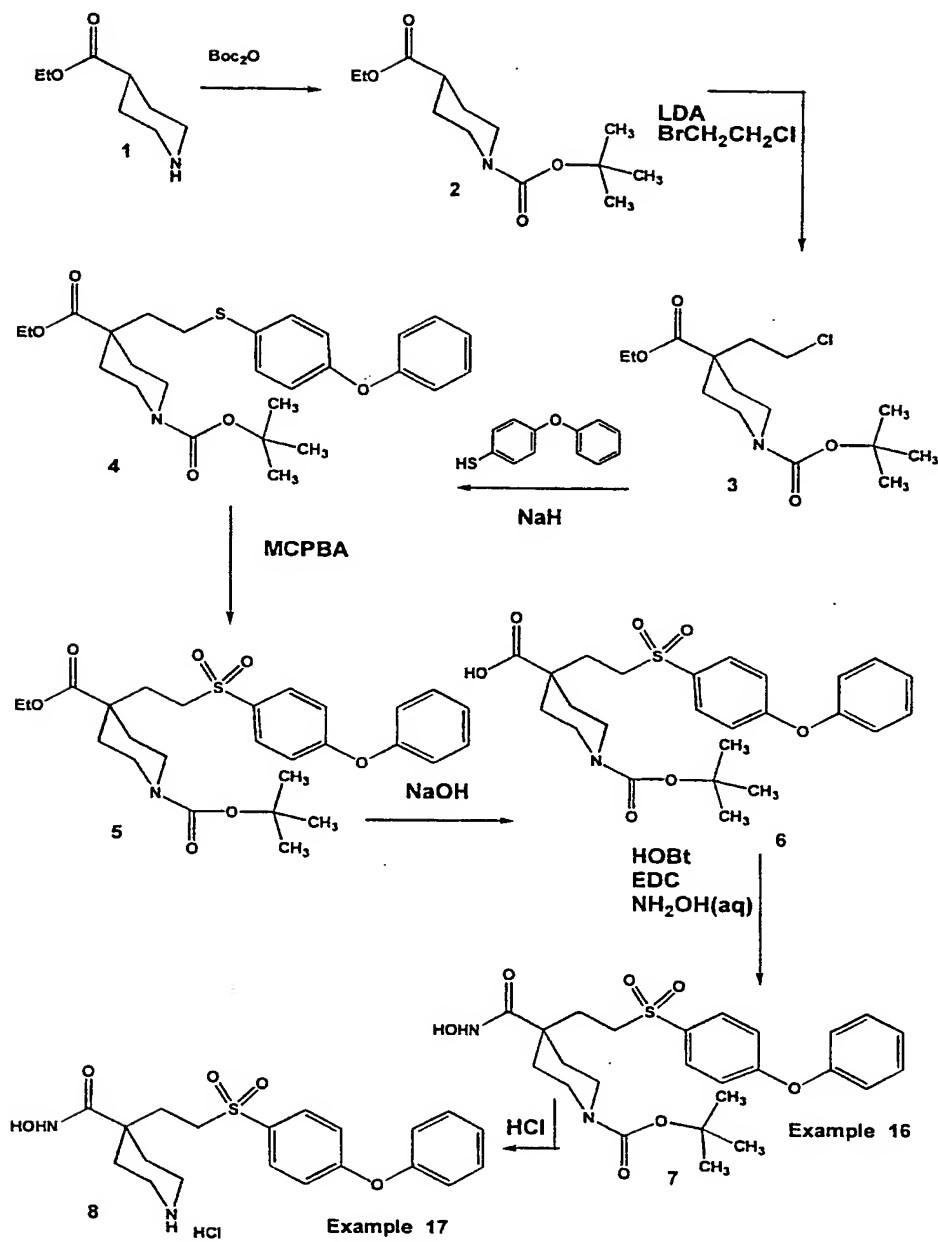
-121-

Scheme 6B



-122-

Scheme 7



-123-

Treatment Process

A process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity is also contemplated. That 5 process comprises administering a compound described hereinbefore in an MMP enzyme-inhibiting effective amount to a mammalian host having such a condition. The use of administration repeated a plurality of times is particularly contemplated.

10 A contemplated compound is used for treating a host mammal such as a mouse, rat, rabbit, dog, horse, primate such as a monkey, chimpanzee or human that has a condition associated with pathological matrix metalloprotease activity.

15 Also contemplated is the similar use of a contemplated compound in the treatment of a disease state that can be affected by the activity of metalloproteases such as TNF- α convertase. Exemplary of such disease states are the acute phase responses 20 of shock and sepsis, coagulation responses, hemorrhage and cardiovascular effects, fever and inflammation, anorexia and cachexia.

In treating a disease condition associated with pathological matrix metalloproteinase activity, 25 a contemplated MMP inhibitor compound can be used, where appropriate, in the form of an amine salt derived from an inorganic or organic acid. Exemplary acid salts include but are not limited to the following: acetate, adipate, alginate, citrate, 30 aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate,

-124-

hemisulfate, heptanoate, hexanoate, fumarate,
hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-
ethanesulfonate, lactate, maleate, methanesulfonate,
nicotinate, 2-naphthalenesulfonate, oxalate,
5 palmoate, pectinate, persulfate, 3-phenylpropionate,
picrate, pivalate, propionate, succinate, tartrate,
thiocyanate, tosylate, mesylate and undecanoate.

Also, a basic nitrogen-containing group can
be quaternized with such agents as lower alkyl (C₁-
10 C₆) halides, such as methyl, ethyl, propyl, and butyl
chloride, bromides, and iodides; dialkyl sulfates
like dimethyl, diethyl, dibutyl, and diamyl sulfates,
long chain (C₈-C₂₀) halides such as decyl, lauryl,
myristyl and dodecyl chlorides, bromides and iodides,
15 aralkyl halides like benzyl and phenethyl bromides,
and others to provide enhanced water-solubility.
Water or oil-soluble or dispersible products are
thereby obtained as desired. The salts are formed by
combining the basic compounds with the desired acid.

20 Other compounds useful in this invention
that are acids can also form salts. Examples include
salts with alkali metals or alkaline earth metals,
such as sodium, potassium, calcium or magnesium or
with organic bases or basic quaternary ammonium
25 salts.

In some cases, the salts can also be used
as an aid in the isolation, purification or
resolution of the compounds of this invention.

Total daily dose administered to a host
30 mammal in single or divided doses of an MMP enzyme-
inhibiting effective amount can be in amounts, for
example, of about 0.001 to about 100 mg/kg body
weight daily, preferably about 0.001 to about 30

-125-

mg/kg body weight daily and more usually about 0.01 to about 10 mg. Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. A suitable dose can be administered, in 5 multiple sub-doses per day. Multiple doses per day can also increase the total daily dose, should such dosing be desired by the person prescribing the drug.

The dosage regimen for treating a disease condition with a compound and/or composition of this 10 invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, 15 efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed can vary widely 20 and therefore can deviate from the preferred dosage regimen set forth above.

A compound useful in the present invention can be formulated as a pharmaceutical composition. Such a composition can then be administered orally, 25 parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of 30 transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal

-126-

injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co. (Easton, Pennsylvania: 1975) and Liberman, H.A. 5 and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, (New York, N.Y.: 1980).

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using 10 suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among 15 the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland 20 fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, 25 polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a 30 suitable nonirritating excipient such as cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are sold at ordinary temperatures but liquid at the rectal

-127-

temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and 5 granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds can be admixed with lactose, sucrose, 10 starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or 15 polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of 20 capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

25 For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or 30 granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol,

-128-

ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

5 Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise
10 adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

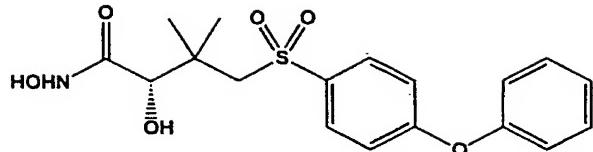
15 The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

Best Mode for Carrying Out the Invention

20 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely
25 illustrative, and not limiting of the remainder of the disclosure in any way whatsoever.

Example 1: (S)-N,2-dihydroxy-3,3-dimethyl-4-
[(phenoxyphenyl)sulfonyl]butanamide

-129-

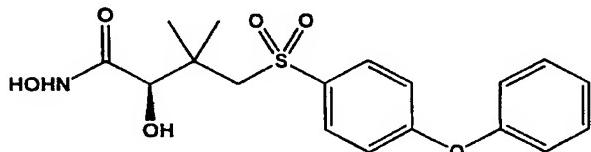


Part A: To a solution of 4-(phenoxy)benzenethiol (13.3 g, 65.8 mmol) in DMF (100 mL) was added K₂CO₃ (9.1 g, 65.8 mmol). To this solution was added S-pantolactone (8.5 g, 65.3 mmol) and the solution was heated to one hundred degrees Celsius for 4 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and 1N HCl. The organic layer was washed with saturated NaCl and dried over MgSO₄. To a solution of the crude sulfide in methanol (200 mL) and H₂O (50 mL) was added Oxone® (121 g) and the mixture stirred for 18 hours. The mixture was filtered and the filtrate was partitioned between ethyl acetate and H₂O. The organic layer was dried over MgSO₄. A solution of the crude sulfone in methanol was treated with thionyl chloride (4.8 mL, 65.8 mmol) and the solution was heated to reflux for 1 hour. Concentration in vacuo provided the methyl ester sulfone as a white solid (13.0 g, 53 %).

Part B: To a solution of the methyl ester sulfone of part A (780 mg, 2.06 mmol) in THF (10 mL) and methanol (10 mL) was added 50% aqueous NH₂OH (2.4 mL, 41.2 mmol). The solution stirred for 3 days and then concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as a white solid (300 mg, 38 %). HPLC purity: 98.8 %. MS(CI) MH⁺ calculated for C₁₈H₂₁NO₆S: 380, found 380.

-130-

Example 2: (R)-N,2-dihydroxy-3,3-dimethyl-4-[(4-phenoxyphenyl)sulfonyl]butanamide



5

Part A: To a solution of 4-(phenoxy)benzenethiol (9.8 g, 48.5 mmol) in DMF was added K₂CO₃ (6.7 g, 48.5 mmol) followed by R-10 pantolactone (6.3 g, 48.4 mmol). The solution was heated to one hundred degrees Celsius for 3 hours followed by concentration in vacuo. The residue was partitioned between ethyl acetate and 1N HCl. The organic layer was dried over MgSO₄ and concentrated in 15 vacuo. To a solution of the crude sulfide in methanol (200 mL) and H₂O (50 mL) was added Oxone® (90 g, 145 mmol) and the solution was stirred for 18 hours. The mixture was filtered and the filtrate was concentrated and partitioned between ethyl acetate 20 and H₂O. The organic layer was concentrated and dried over MgSO₄. After concentration in vacuo the residue was dissolved in methanol and treated with thionyl chloride (3.54 mL, 48.5 mmol). The solution was heated to reflux for 1 hour. Concentration in vacuo 25 provided the methyl ester sulfone as a white solid (8.45 g, 54 %).

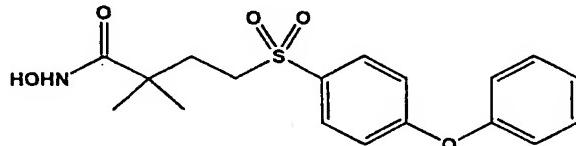
Part B: To a solution of the methyl ester sulfone of part A (460 mg, 1.2 mmol) in THF (5 mL) and methanol (5 mL) was added 50% aqueous NH₂OH (1 30 mL). The solution stirred for 4 days at ambient

-131-

temperature and 3 days at fifty degrees Celsius. Concentration in vacuo followed by reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as a white solid (95 mg, 21 %).
5 MS(CI) MH⁺ calculated for C₁₈H₂₁NO₆S: 380, found 380.

Example 3: 2,2-dimethyl-N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]butanamide

10



Part A: To a solution of diisopropylamine (2.24 mL, 16 mmol) in tetrahydrofuran (15 mL) cooled to zero degrees Celsius was added n-butyllithium (1.6 M in hexanes, 10 mL) over 2 minutes. The solution was cooled to minus seventy-eight degrees Celsius and methyl isobutyrate (1.60 mL, 14 mmol) was added.
15 After 30 minutes 1-bromo-2-chloroethane (1.3 mL, 16 mmol) was added. The cooling bath was removed and the mixture was allowed to stir at ambient temperature for 2.5 hours. The solution was concentrated, diluted with 1N HCl and extracted with chloroform. The organic layer was dried over MgSO₄ and filtered through silica. Concentration in vacuo
20 provided the crude chloride compound as a volatile oil (431 mg, 19%) and was used without further purification.
25

Part B: To a solution of sodium hydride (60% dispersion in mineral oil, 104 mg, 2.6 mmol) in acetonitrile (10 mL) cooled to zero degrees Celsius

-132-

was added 4-(phenoxy)benzenethiol (0.53 g, 2.6 mmol). After the solution was stirred for 10 minutes, the chloride compound of part A (431 mg, 2.6 mmol) was added. The bath was removed and the reaction mixture 5 was stirred overnight at ambient temperature.

Concentration *in vacuo* followed by chromatography provided the sulfide as an oil (474 mg, 54%).

Part C: To a solution of the sulfide of part B (474 mg, 1.4 mmol) in glacial acetic acid (5 mL) was 10 added 30% hydrogen peroxide (0.6 mL, 6 mmol) and the mixture was heated over a steam bath for 40 minutes. Lyophilization followed by chromatography (hexane/ethyl acetate) provided the sulfone as an oil (469 mg, 90%).

15 Part D: To a solution of the sulfone of part A (460 mg, 1.3 mmol) in 95% ethanol (5 mL) was added KOH (150 mg) and the solution was warmed to reflux. After 1.5 hours, the reaction was cooled to ambient temperature and adjusted to pH 4-5 using conc. HCl.

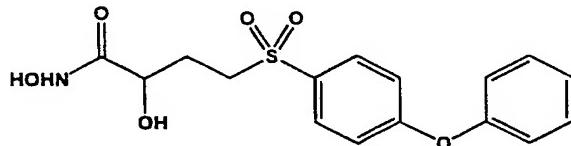
20 The mixture was diluted with acetonitrile, then concentrated to dryness. The resulting acid was diluted with acetonitrile (4 mL) and O-tetrahydropyranyl hydroxylamine (176 mg, 1.5 mmol) was added, followed by 1-(3-dimethylaminopropyl)-3-25 ethylcarbodiimide hydrochloride (0.288 g, 1.5 mmol). The mixture was stirred overnight, then diluted with water and extracted with chloroform. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Chromatography provided the ester as an oil (421 mg, 30 73%).

Part E: To a solution of the ester of part D (421 mg, 0.95 mmol) in methanol (10 mL) was added toluenesulfonic acid (56 mg) and the solution was

-133-

stirred 90 minutes at ambient temperature.
Concentration *in vacuo* followed by chromatography (on
silica, chloroform/methanol/ammonium hydroxide)
provided the title compound as a white glass (237 mg,
5 69%). Analytical calculation for C₁₈H₂₁NO₅S•H₂O: C,
56.68; H, 6.08; N, 3.67. Found: C, 56.34; H, 5.52; N,
3.61.

Example 4: N,2-dihydroxy-4-[(4-phenoxyphenyl)-
10 sulfonylbutanamide



Part A: To a solution of 4-fluorothiophenol
15 (10.0 g, 78.02 mmol) and 3-chloro-1-propanol (7.2 mL,
85.82 mmol) in DMF (80 mL) was added K₂CO₃ (32.4 g,
234.06 mmol). The solution stirred for 2 hours at
ambient temperature. After concentration *in vacuo*
the residue was partitioned between ethyl acetate and
20 H₂O and the organic layer was washed with saturated
NaCl and dried over MgSO₄. Concentration *in vacuo*
provided a colorless oil. To a solution of the oil
in methanol (300 mL) and H₂O (60 mL) was added
Oxone®. The solution stirred for 2 hours. After
25 filtration to remove excess Oxone® the filtrate was
concentrated *in vacuo* and the residue was dissolved
into H₂O and extracted with ethyl acetate. The
combined organic layers were washed with saturated
NaHCO₃ and saturated NaCl and dried over MgSO₄.

-134-

Concentration *in vacuo* provided the sulfone as a colorless oil (15.7 g, 92%).

Part B: To a solution of the sulfone of part A (12.7 g, 58.2 mmol) and phenol (16.4 g, 174.6 mmol) in DMF (100 mL) was added K₂CO₃ (24.1 g, 174.6 mmol) and the slurry stirred at one hundred degrees Celsius for 18 hours. The slurry was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and H₂O. The organic layer was washed with 1N HCl, saturated NaHCO₃ and saturated NaCl, and dried over MgSO₄. Chromatography (on silica, ethyl acetate/hexane) provided the phenoxy compound as a pinkish solid (12.3 g, 72%).

Part C: To a solution of the phenoxy of part B (13.0 g, 44.5 mmol) in dichloromethane (60 mL) cooled to zero degrees Celsius, was added triethylamine (25 mL, 18.0 mmol). To this solution was added a solution of SO₃•pyridine (28.3 g, 177.9 mmol) in DMSO (60 mL) dropwise. The solution stirred for 2 hours at zero degrees Celsius. The solution was quenched in ice and extracted with ethyl acetate. The organic layer was washed with 5% KHSO₄ and saturated NaCl and dried over MgSO₄. Concentration *in vacuo* provided the aldehyde as a tan solid (12.7 g, 98%).

Part D: To a solution of the aldehyde of part C (12.9 g, 44.43 mmol) in dichloromethane (150 mL) cooled to zero degrees Celsius was added trimethylsilyl cyanide (6.6 g, 66.65 mmol) and zinc bromide (15.0 g, 66.65 mmol). The solution was stirred for 3 hours. The mixture was concentrated *in vacuo* and partitioned between ethyl acetate and 2N HCl. The organic layer was washed with saturated NaHCO₃ and saturated NaCl and dried over MgSO₄.

-135-

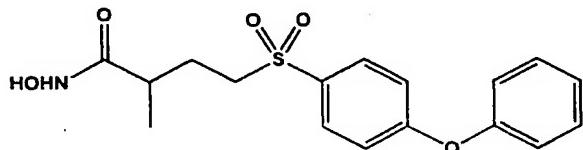
Chromatography (on silica, ethyl acetate/CH₂Cl₂) provided the cyano compound as a white solid (10.3 g, 73 %).

Part E: To a solution of the cyano compound of 5 part D (10.3 g, 32.3 mmol) in glacial acetic acid (30 mL) was added 6N HCl (100 mL). The solution heated at ninety degrees Celsius for 2 hours. The solution was concentrated *in vacuo* to dryness to provide the acid as a tan solid (9.1 g, 71%).

Part F: To a solution of the acid of part E (2.0 g, 5.9 mmol) and N-hydroxybenzotriazole (1.0 g, 7.14 mmol) in DMF was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.3 g, 6.54 mmol). After 1 hour of 10 stirring at ambient temperature 50% aqueous NH₂OH (1.1 mL, 17.8 mmol) and 4-methylmorpholine (2.0 mL, 17.8 mmol) were added. The solution was stirred for 1 hour. The solution was concentrated *in vacuo* and partitioned between ethyl acetate and 1N HCl and the 15 organic layer was washed with saturated NaHCO₃ and saturated NaCl and dried over Na₂SO₄. Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as a white solid (100 mg, 5 %). MS(CI) MH⁺ calculated for C₁₆H₁₇NO₆S: 352, found 352.

20

Example 5: N-hydroxy-2-methyl-4-[(4-phenoxypyhenyl)sulfonyl]butanamide



-136-

Part A: To a solution of NaH (60% suspension in mineral oil, 0.88 g, 22 mmol) in THF (20 mL) cooled to zero degrees Celsius was added 4-(phenoxy)benzenethiol (4.04 g, 20 mmol). After 10 minutes, ethanol (5 mL) was added, followed by α -methyl- γ -butyrolactone (2.38 g, 25 mmol), and the reaction mixture was warmed to reflux. After 20 hours, the mixture was cooled and concentrated. The residue was diluted with water and acidified with concentrated HCl. The aqueous mixture was extracted with chloroform and the organic layer was dried over MgSO₄ and concentrated *in vacuo*. Chromatography (on silica, hexane/ethyl acetate) provided the sulfide as an oil (3.74 g, 62%). MS(CI) MH⁺ calculated for C₁₇H₁₈O₃S: 303, found: 303.

Part B: To a solution of the sulfide of part A (3.74 g, 12.4 mmol) in glacial acetic acid (25 mL) was added 30% hydrogen peroxide (4.8 mL, 48 mmol). The solution was heated over a steam bath for 40 minutes. Lyophilization followed by chromatography provided the sulfone as a wax (3.62 g, 89%).

Part C: To a solution of the sulfone of part B (2.40 g, 7.2 mmol) in acetonitrile (10 mL) was added O-tetrahydropyranyl hydroxylamine (0.90 g, 7.7 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.48g, 7.7 mmol). The mixture was stirred overnight, then diluted with water and extracted with chloroform. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Chromatography provided the ester as an oil (2.23 g, 71% yield).

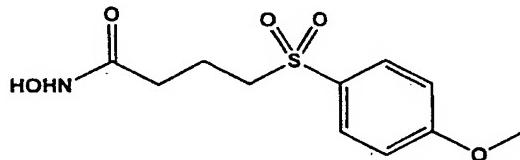
Part D: To the ester of part C (2.23 g, 5.11 mmol) in methanol (60 mL) was added p-toluenesulfonic

-137-

acid (1.2 g) and the solution was stirred 40 minutes. Following neutralization with concentrated ammonium hydroxide, chromatography (on silica, chloroform/methanol/ammonium hydroxide) provided the 5 title compound as a white wax (981 mg, 54%). Analytical calculation for $C_{17}H_{19}NO_5S \cdot 0.5H_2O$: C, 56.97; H, 5.62; N, 3.91. Found: C, 56.90; H, 5.22; N, 4.02.

Example 6: N-hydroxy-4-[(4-methoxyphenyl)-

10 sulfonylbutanamide



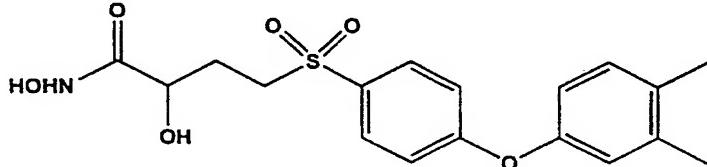
Part A: To a solution of 4-methoxybenzenethiol 15 (2.5 g, 17.83 mmol) and ethyl 4-bromobutyrate (3.5 g, 17.83 mmol) in ethanol (50 mL) was cooled on an ice bath and triethylamine (2.73 mL, 19.61 mmol) was added. The solution stirred for 6 hours at ambient temperature. To this solution was added H₂O (10 mL) 20 and Oxone® (22 g, 35.7 mmol) and the solution stirred for 20 hours. The solution was filtered to remove excess Oxone® and the filtrate was concentrated in vacuo. The residue was dissolved into H₂O and extracted with ethyl acetate. The combined organic 25 layers were washed with saturated NaHCO₃ and saturated NaCl and dried over MgSO₄. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a white solid (2.41 g, 47%). HPLC purity: 97%.

Part B: To a solution of the sulfone of part A 30 (2.41 g, 8.42 mmol) and hydroxylamine hydrochloride

-138-

(700 mg, 10.10 mmol) in methanol (50 mL), cooled to zero degrees Celsius, was added Na metal (470 mg, 20.20 mmol). After stirring at ambient temperature for 2 hours, the reaction was quenched by the 5 addition of dry ice to pH=7. Following concentration *in vacuo* the residue was dissolved into H₂O and acidified to pH=3 with 2N HCl. The solution was extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl and dried over 10 Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the title compound as a white solid (300 mg, 13%). HPLC purity: 98.7%. HRMS calculated for C₁₁H₁₅NO₅S: 274.0749, found 274.0779.

15 Example 7: (+/-)-4-[[4-(3,4-dimethylphenoxy)phenyl]-
sulfonyl-N,2-dihydroxybutanamide



20

Part A: To a solution of 4-fluorothiophenol (20 g, 156 mmol) in DMF (100 mL) was added 3-chloro-1-propanol (11.5 g, 121 mmol) and K₂CO₃ (64.7 g, 468 mmol) and the mixture was stirred for 18 hours. The 25 solution was removed by concentration *in vacuo* and the residue was partitioned between ethyl acetate and H₂O. The organic layer was extracted 3 times with ethyl acetate and the combined organics were washed with saturated NaCl and dried over Na₂SO₄.

-139-

Concentration in vacuo provided the sulfide as an amber oil (30.53 g).

Part B: To a solution of the sulfide of part A (30.5 g) in methanol (450 mL) and H₂O (50 mL) was 5 added Oxone® (262 g, 426 mmol) and the mixture was stirred for 18 hours. The mixture is filtered to collect the excess solids and the filtrate was concentrated in vacuo. The residue was partitioned between ethyl acetate and H₂O and the organic layer 10 was washed with 5% NaHCO₃ and saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the sulfone as an amber oil (22.04 g, 83 %, 2 steps).

Part C: To a solution of the sulfone of part B (22.04 g, 101 mmol) in DMF (50 mL). To this solution 15 is added 3,4-dimethylphenol (18.62 g, 152 mmol) in DMF (50 mL) followed by K₂CO₃ (43.13 g, 312 mmol) and the solution was heated at one hundred ten degrees Celsius for 17 hours. The solution was partitioned between ethyl acetate and H₂O and the organic layer 20 was washed with 1N HCl, 5% NaHCO₃, and NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the dimethylphenoxyphenol as a white solid (15.17 g, 47 %).

Part D: To a solution of dimethylphenoxyphenol 25 of part C (15.17 g, 47.4 mmol) in dichloromethane (80 mL) was added triethylamine (20 mL) followed by pyridine•SO₃ (22.46 g, 141 mmol) in DMSO (80 mL) added dropwise. The solution was stirred for 1 hour. The reaction was quenched by the addition of crushed ice 30 and concentrated in vacuo to remove the solvent. The solution was extracted with ethyl acetate and the organic layer was washed with saturated NaCl and

-140-

dried over MgSO₄. Concentration in vacuo provided the aldehyde as an orange oil (15.03 g).

Part E: To a solution of the aldehyde of part D (15.6 g) in dichloromethane (100 mL) was added 5 trimethylsilyl cyanide (7.3 mL, 71.1 mmol) followed by zinc iodide (2.27 g, 7.1 mmol) and the solution was stirred on an ice bath for 17 hours. The solution is partitioned between ethyl acetate and 2M HCl. The organic layer was washed with H₂O and 10 saturated NaCl and dried over MgSO₄. Filtration through a silica pad provided the nitrile as an amber oil (14.13 g).

Part F: A solution of the nitrile of part E (14.13 g) in glacial acetic acid (50 mL) and 15 concentrated HCl (50 mL) was heated to one hundred ten degrees Celsius for 2 hours and was stirred for 18 hours. The solution was concentrated in vacuo to provide the acid as a brown oil (13.53 g, 75%, three steps).

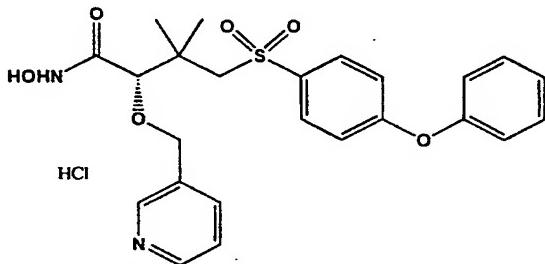
20 Part G: To a solution of the acid of part F (13.5 g, 35.7 mmol) in methanol (100 mL) cooled to zero degrees Celsius was added thionyl chloride (4.1 mL, 56.2 mmol) dropwise and the solution is stirred at ambient temperature for 72 hours. The solution 25 was concentration in vacuo and the residue was dissolved into ethyl acetate and washed with 5% NaHCO₃ and saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the methyl ester as a white solid (14.51 g, 30 quantitative yield).

Part H: To a solution of the methyl ester of part G (630 mg, 1.6 mmol) in THF (30 mL) was added 50% aqueous hydroxylamine (1 mL) and the solution was

-141-

stirred for 140 hours. The solution is concentrated and the residue was dissolved into ethyl acetate and washed with 5% NaHCO₃ and dried over Na₂SO₄. Concentration in vacuo provided the title compound as
5 a white solid (450 mg, 69 %). MS(CI) MH⁺ calculated for C₁₈H₂₁NO₆S: 380, found 380.

Example 8: (S)-N-hydroxy-3,3-dimethyl-4-[(4-phenoxyphenyl)sulfonyl]-2-(3-pyridinylmethoxy) butanamide
10 monohydrochloride



15 Part A: To a solution of 4-(phenoxy)benzenethiol (13.3 g, 65.8 mmol) in DMF (100 mL) was added K₂CO₃ (9.1 g, 65.8 mmol). To this solution was added S-pantolactone (8.5 g, 65.3 mmol) and the solution was heated to one hundred degrees
20 Celsius for 4 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and 1N HCl. The organic layer was washed with saturated NaCl and dried over MgSO₄. To a solution of the crude sulfide in methanol (200 mL)
25 and H₂O (50 mL) was added Oxone® (121 g) and the mixture stirred for 18 hours. The mixture was filtered and the filtrate was partitioned between ethyl acetate and H₂O. The organic layer was dried

-142-

over MgSO₄. A solution of the crude sulfone in methanol was treated with thionyl chloride (4.8 mL, 65.8 mmol) and the solution was heated to reflux for 1 hour. Concentration in vacuo provided the methyl ester sulfone as a white solid (13.0 g, 53 %).

Part B: To DMF (12 mL) was added NaH (60% suspension in mineral oil, 255 mg, 10.6 mmol) followed by the methyl ester sulfone of part A (2.00 g, 5.28 mmol). To a solution of 3-picoly l chloride hydrochloride (868 mg, 5.28 mmol) in DMF (12 mL) was added NaH (60% suspension in mineral oil, 257 mg, 10.7 mmol). After 5 minutes the solution of the sulfone was added to this solution of the chloride and the mixture stirred for 18 hours at ambient temperature. The reaction was quenched by the addition of H₂O and the solution was concentrated in vacuo. The residue was dissolved into ethyl acetate and H₂O and the aqueous is extracted twice with ethyl acetate. The combined organic layers are washed with saturated NaHCO₃ and saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the ether as a solid (950 mg, 38 %).

Part C: To a solution of the ether of part B (950 mg, 2.0 mmol) in glacial acetic acid (15 mL) was added concentrated HCl (15 mL) and the solution was heated to reflux for 3 hours. The solution was concentrated in vacuo provided the acid as a white foam (1.05 g, quantitative yield).

Part D: To a solution of the acid of part C (1.03 g, 2.0 mmol) in DMF (10 mL) was added N-hydroxybenzotriazole (301 mg, 2.2 mmol), 4-methylmorpholine (1.02 mL, 10 mmol), O-

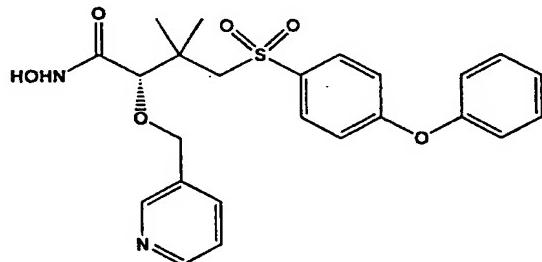
-143-

tetrahydropyranyl hydroxylamine (725 g, 6.2 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (500 mg, 2.6 mmol). The solution was stirred for 20 hours at ambient temperature. The 5 solution was partitioned between ethyl acetate and H₂O and the organic layer was washed with saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the ester as a white solid (890 mg, 82%).

10 Part E: To a solution of the ester of part D (890 mg, 1.6 mmol) in 4M HCl in dioxane (5 mL) was added methanol (12 drops) and the solution was stirred for 30 minutes. The solution was concentrated *in vacuo* and reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as a white solid (540 mg, 66%). MS(CI) MH⁺ calculated for C₂₄H₂₆N₂O₆S: 471, found 471.

15 Example 8a: Preparation of (S)-N-hydroxy-3,3-dimethyl-

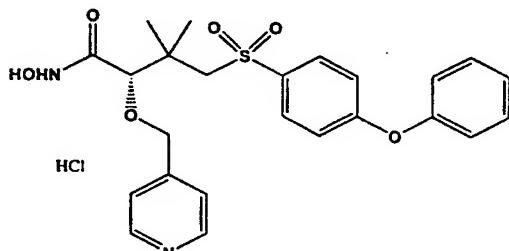
20 4-[(4-phenoxyphenyl)sulfonyl]-2-(3-pyridinylmethoxy) butanamide



A solution of the HCl salt of example 8 in 25 saturated NaHCO₃ was extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na₂SO₄. Concentration *in vacuo* provided the title compound.

-144-

Example 9: (S)-N-hydroxy-3,3-dimethyl-4-[(4-phenoxyphenyl)sulfonyl]-2-(4-pyridinylmethoxy)butanamide monohydrochloride



5

Part A: To a solution of 4-(phenoxy)benzenethiol (13.3 g, 65.8 mmol) in DMF (100 mL) was added K₂CO₃ (9.1 g, 65.8 mmol). To this
 10 solution was added S-pantolactone (8.5 g, 65.3 mmol) and the solution was heated to 100° C for 4 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and 1N HCl. The organic layer was washed with saturated NaCl and dried over MgSO₄. To a solution of the crude sulfide in methanol (200 mL) and H₂O (50 mL) was added Oxone® (121 g) and the mixture stirred for 18 hours. The mixture was filtered and the filtrate was partitioned between ethyl acetate and H₂O. The
 15 organic layer was dried over MgSO₄. A solution of the crude sulfone in methanol was treated with thionyl chloride (4.8 mL, 65.8 mmol) and the solution was heated to reflux for 1 hour. Concentration in vacuo provided the methyl ester sulfone as a white solid
 20 (13.0 g, 53 %).

Part B: To DMF (12 mL) was added NaH (60% suspension in mineral oil, 253 mg, 10.6 mmol) followed by the methyl ester sulfone of part A (2.00

-145-

g, 5.28 mmol). To a solution of 4-picoly1 chloride hydrochloride (868 mg, 5.28 mmol) in DMF (12 mL) was added NaH (60% suspension in mineral oil, 255 mg, 10.7 mmol). After 5 minutes the solution of the sulfone was added to this solution of the chloride and the mixture stirred for 18 hours at ambient temperature. The reaction was quenched by the addition of H₂O and the solution was concentrated *in vacuo*. The residue was dissolved into ethyl acetate and H₂O and the aqueous was extracted twice with ethyl acetate. The combined organic layers were washed with saturated NaHCO₃, and saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the ether as a solid (1.07 mg, 43 %).

Part C: To a solution of the ether of part B (1.07 mg, 2.15 mmol) in glacial acetic acid (15 mL) was added concentrated HCl (15 mL) and the solution was heated to reflux for 3 hours. The solution was concentrated *in vacuo* provided the acid as a white foam (1.09 mg, quantitative yield).

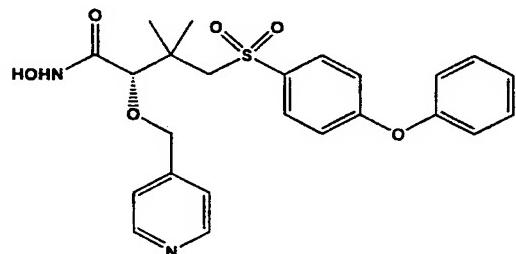
Part D: To a solution of the acid of part C (1.09 g, 2.0 mmol) in DMF (10 mL) was added N-hydroxybenzotriazole (301 mg, 2.2 mmol), 4-methylmorpholine (1.02 mL, 10 mmol), O-tetrahydropyranyl hydroxylamine (725 g, 6.2 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (500 mg, 2.6 mmol). The solution stirred for 20 hours at ambient temperature. The solution was partitioned between ethyl acetate and H₂O and the organic layer was washed with saturated NaCl and dried over Na₂SO₄. Chromatography (on silica,

-146-

ethyl acetate/hexane) provided the ester as a white solid (840 mg, 77 %).

Part E: To a solution of the ester of part D (840 mg, 1.5 mmol) in 4M HCl in dioxane (5 mL) was 5 added methanol (12 drops) and the solution was stirred for 30 minutes. The solution was concentrated *in vacuo* and reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as a white solid (350 mg, 45 %).
10 MS(CI) MH⁺ calculated for C₂₄H₂₆N₂O₆S: 471, found 471.

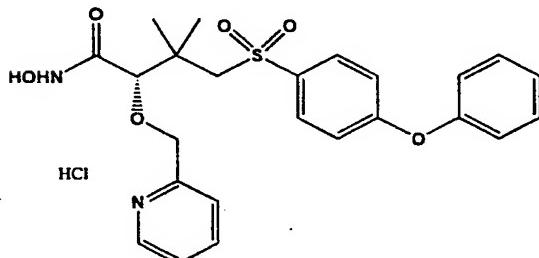
Example 9a: (S)-N-hydroxy-3,3-dimethyl-4-[(4-phenoxyphenyl)sulfonyl]-2-(4-pyridinylmethoxy)butanamide
15



20 A solution of the HCl salt of example 9 in saturated NaHCO₃ was extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na₂SO₄. Concentration *in vacuo* provided the title compound.
25

-147-

Example 10: (S)-N-hydroxy-3,3-dimethyl-4-[(4-phenoxyphenyl)sulfonyl]-2-(2-pyridinylmethoxy)butanamide monohydrochloride



5

Part A: To a solution of 4-(phenoxy)benzenethiol (13.3 g, 65.8 mmol) in DMF (100 mL) was added K₂CO₃ (9.1 g, 65.8 mmol). To this
 10 solution was added S-pantolactone (8.5 g, 65.3 mmol) and the solution was heated to one hundred degrees Celsius for 4 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and 1N HCl. The organic layer was
 15 washed with saturated NaCl and dried over MgSO₄. To a solution of the crude sulfide in methanol (200 mL) and H₂O (50 mL) was added Oxone® (121 g) and the mixture stirred for 18 hours. The mixture was filtered and the filtrate was partitioned between
 20 ethyl acetate and H₂O. The organic layer was dried over MgSO₄. A solution of the crude sulfone in methanol was treated with thionyl chloride (4.8 mL, 65.8 mmol) and the solution was heated to reflux for 1 hour. Concentration in vacuo provided the methyl
 25 ester sulfone as a white solid (13.0 g, 53 %).

Part B: To a solution of the methyl ester sulfone (21.1 g, 57.8 mmol) in methanol (120 mL) was added thionyl chloride (5.1 mL, 69.5 mmol) and the

-148-

solution was heated to reflux for 1 hour. The solution was concentrated and the residue was dissolved into ethyl acetate and washed with saturated NaHCO₃, H₂O, and saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the methyl ester as a solid (13.3 g, 61 %).

Part C: To a slurry of NaH (60% suspension in mineral oil, 253 mg, 6.32 mmol) in DMF (12 mL) was slowly added the alcohol of part B (2.0 g, 5.28 mmol) and the mixture was stirred for 30 minutes. To a slurry of NaH (60% suspension in mineral oil, 253 mg, 6.32 mmol) in DMF (12 mL) was added 2-picoyl chloride hydrochloride (868 mg, 5.28 mmol). This solution was added to the first mixture dropwise and the solution was stirred for 18 hours. The reaction was quenched with H₂O and the solvent was removed by concentration *in vacuo*. The residue was partitioned between ethyl acetate and H₂O. The organic layer was washed with saturated NaHCO₃ and saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, methyl acetate/hexane) provided the ether as an oil (1.32 g, 53%).

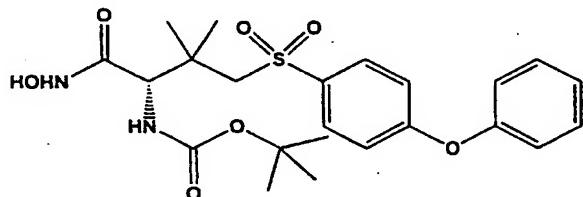
Part D: A solution of the ether of part C (1.0 g, 2.0 mmol) in acetic acid (15 mL) and concentrated HCl (15 mL) was heated to reflux for 3.5 hours. The solution was concentrated *in vacuo* to provide the acid as an off-white foam (910 mg, 92 %).

Part E: To a solution of the acid of part D (910 mg, 1.86 mmol) in DMF (10 mL) was added N-hydroxybenzotriazole (301 mg, 2.23 mmol), 4-methylmorpholine (1.02 mL, 9.3 mmol), O-tetrahydropyranyl hydroxylamine (675 mg, 5.7 mmol)

-149-

- and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (499 mg, 2.60 mmol) and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue 5 was partitioned between ethyl acetate and H₂O. The organic layer was washed with H₂O and saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the ester as a foam (910 mg, 88 %).
- 10 Part F: A solution of the ester of part E (910 mg, 1.64 mmol) in 4M HCl (5 mL) and methanol (12 drops) was stirred for 30 minutes. The solution was concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title 15 compound as a white solid (260 mg, 33 %). MS(CI) MH⁺ calculated for C₂₄H₂₆N₂O₆S: 471, found 471.

Example 11: (S)-1,1-dimethylethyl [1-[(hydroxyamino)- 20 carbonyl-2,2-dimethyl-3-[(4-phenoxyphenyl)-sulfonylpropyl]carbamate



Part A: To a solution of 4-
25 (phenoxy)benzenethiol (9.8 g, 48.5 mmol) in DMF was added K₂CO₃ (6.7 g, 48.5 mmol) followed by R-pantolactone (6.3 g, 48.4 mmol). The solution was heated to one hundred degrees Celsius for 3 hours followed by concentration in vacuo. The residue was

-150-

partitioned between ethyl acetate and 1N HCl. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. To a solution of the crude sulfide in methanol (200 mL) and H₂O (50 mL) was added Oxone® (90 g, 145 mmol) and the solution was stirred for 18 hours. The mixture was filtered and the filtrate was concentrated and partitioned between ethyl acetate and H₂O. The organic layer was concentrated and dried over MgSO₄. After concentration *in vacuo* the residue 5 was dissolved in methanol and treated with thionyl chloride (3.54 mL, 48.5 mmol). The solution was heated to reflux for 1 hour. Concentration *in vacuo* provided the methyl ester sulfone as a white solid 10 (8.45 g, 54 %).

15 Part B: To a solution of the methyl ester sulfone of part A (4.0 g, 10.57 mmol) in dichloromethane (50 mL) was added pyridine (1.1 mL, 13.33 mmol) and the solution was cooled to minus seventy-five degrees Celsius. To this solution was 20 added triflic anhydride (2.0 mL, 11.63 mmol) dropwise. The solution was stirred at ambient temperature for 2 hours. The solution was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and H₂O. The organic layer was 25 washed with saturated NaHCO₃, and saturated NaCl and dried over Na₂SO₄. Concentration *in vacuo* provided the triflate as a colored oil (5.4 g, quantitative yield).

30 Part C: To a solution of the triflate of part B (5.4 g, 10.58 mmol) in toluene (100 mL) was added n-butyl ammonium azide (3.3 g, 11.64 mmol) and the solution was stirred at ambient temperature for 20 hours. The solution was concentrated *in vacuo* and

-151-

the residue was partitioned between ethyl acetate and H₂O. The organic layer was washed with saturated NaHCO₃, 5% citric acid and saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the 5 azide as an orange oil (7.4 g).

Part D: To a solution of the azide of part C (4.3 g, 10.58 mmol) and p-toluenesulfonic acid monohydrate (2.0 g, 10.58 mmol) in methanol (80 mL) was added 4% Pd/C and the solution was stirred for 1 10 hour under H₂ at 50 psi. The solution continued to stir for 18 hours. The mixture was filtered through Celite and the filtrate was concentrated in vacuo to provide the crude amine p-toluenesulfonic acid salt as a colored oil (9.3 g).

Part E: To a solution of the crude amine salt of part D (5.8 g, 10.55 mmol) in THF (100 mL) was added di-t-butyl dicarbonate (2.5 g, 11.61 mmol) and triethylamine (3.2 mL, 23.21 mmol). The solution was stirred at ambient temperature for 18 hours. The 20 solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and H₂O. The organic layer was washed with 5% KHSO₄ and saturated NaCl and dried over MgSO₄. Chromatography (on silica, ethyl acetate/hexane) provide the protected amine as 25 a white foam (4.0 g, 87 %).

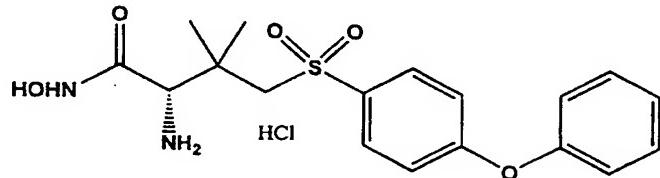
Part F: To a solution of the protected amine of part E (1.0 g, 2.09 mmol) in THF (10 mL) was added LiOH (400 mg, 8.38 mmol) in H₂O (10 mL) and the solution was stirred at ambient temperature for 6 30 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and 5% KHSO₄. The organic layer was washed with saturated and dried over Na₂SO₄. Concentration in vacuo

-152-

provided the acid as a white foam (1.0 g, quantitative yield).

Part G: To a solution of the acid of part F (1.0 g, 2.16 mmol) in DMF (10 mL) was added N-hydroxybenzotriazole (450 mg, 3.24 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (500 mg, 2.59 mmol) and 50% aqueous hydroxylamine (2.5 mL) and was stirred at ambient temperature for 1 hour. The solution was concentrated *in vacuo* and the residue partitioned between ethyl acetate and saturated NaHCO₃. The organic layer was washed with saturated NaCl and dried over Na₂SO₄. Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as a white foam (700 mg, 70 %). HPLC purity: 95 %. MS(CI) MH⁺ calculated for C₂₃H₃₀N₂O₇S: 479, found 479.

Example 12: (S)-2-amino-N-hydroxy-3,3-dimethyl-4-[(4-phenoxyphenyl)sulfonyl]butanamide monohydrochloride

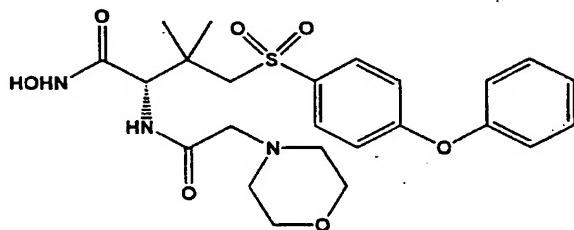


Part A: A solution of the hydroxamate of Example 11, part G (700 mg, 1.46 mmol) in 4M HCl (10 mL) was stirred at ambient temperature for 1 hour. The solution was concentrated *in vacuo* and trituration with ethyl ether provided the title compound as a white foam (600 mg, quantitative yield). HPLC purity:

-153-

93 %. MS(CI) MH⁺ calculated for C₁₈H₂₂N₂O₅S: 379, found 379.

Example 13: (S)-N-[1-[(hydroxyamino)- carbonyl]-2,2-dimethyl-3-[(4-phenoxyphenyl)sulfonyl]-propyl]-4-morpholineacetamide



Part A: A solution of the methyl ester of Example 11, part E (1.84 g, 3.85 mmol) in 4M HCl (20 mL) was stirred at ambient temperature for 1.5 hour. The solution was concentrated *in vacuo* to provide the amine hydrochloride salt as a white foam (1.7 g, quantitative yield).

Part B: To a solution of the amine hydrochloride salt of part A (1.74 g, 4.20 mmol) and diisopropylethylamine (1.7 mL, 9.46 mmol) in dichloromethane (30 mL) cooled to zero degrees Celsius was added chloroacetic anhydride (800 mg, 4.62 mmol) in dichloromethane (10 mL) and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and saturated NaHCO₃. The organic layer was washed with 5% citric acid, H₂O, and saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the chloro compound as an off-white foam (1.5 g, 79 %).

-154-

Part C: To a solution of the chloro compound of part B (1.5 g, 3.30 mmol) in THF (10 mL) and H₂O (5 mL) was added morpholine (1.7 mL, 19.83 mmol) and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and saturated NaHCO₃. The organic layer was washed with saturated NaCl and dried over Na₂SO₄. Concentration *in vacuo* provided the morpholine compound as a white foam (1.6 g, 94 %).

Part D: To a solution of the morpholine compound of part C (1.6 g, 3.17 mmol) in THF (10 mL) was added LiOH (530 mg, 12.68 mmol) in H₂O (10 mL) and the solution was stirred at ambient temperature for 2 hours. The solution was concentrated *in vacuo*. The residue was acidified to pH=6 with dry ice and 5% KHSO₄ and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na₂SO₄. Concentration *in vacuo* provided the acid as a white solid (1.4 g, 88 %).

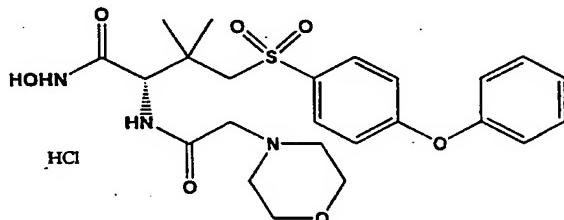
Part E: To a solution of the acid of part D (700 mg, 1.43 mmol) in DMF (10 mL) was added N-hydroxybenzotriazole (300 mg, 2.14 mmol), 4-methylmorpholine (0.5 mL, 4.28 mmol), O-tetrahydropyranyl hydroxylamine (500 mg, 4.42 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (400 mg, 2.14 mmol) and the solution was stirred for 6 hours at ambient temperature. The solution was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and H₂O and the organic layer was washed with saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl

-155-

acetate/hexane/methanol) provided the ester as a white foam (600 mg, 75 %).

Part F: To a solution of the ester of part E (600 mg, 1.02 mmol) in 1,4-dioxane (2 mL) was added 5 4M HCl in dioxane (5 mL) and the solution was stirred for 30 minutes. The solution was concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as an off-white solid (400 mg, 72 %). HPLC purity: 100 %. 10 MS(CI) MH⁺ calculated for C₂₄H₃₁N₃O₇S: 506, found 506. HRMS calculated for C₂₄H₃₁N₃O₇S: 506.1961, found 506.1955.

Example 13a: (S)-N-[1-[(hydroxyamino) carbonyl]-2,2-
15 dimethyl-3-[(4-phenoxyphenyl)sulfonyl]-propyl]-4-morpholineacetamide
monohydrochloride



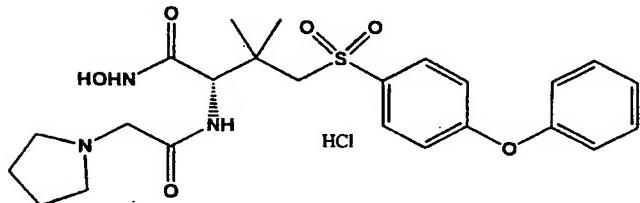
20

To a solution of the hydroxamate of Example 13, part F (360 mg, 0.72 mmol) in acetonitrile (10 mL) was added concentrated HCl (0.15 mL) and the solution was stirred for 10 minutes. Concentration in vacuo followed by trituration with ether provided the 25 hydrochloride salt a pink solid (260 mg, 67 %). HPLC purity: 99.6 %.

Example 14: (S)-N-[1-[(hydroxyamino) carbonyl]-2,2-

-156-

dimethyl-3-[4-phenoxy)sulfonyl]propyl]-1-pyrrolidine acetamide monohydrochloride



5

Part A: To a solution of the chloro compound of Example 13, part B (870 mg, 1.9 mmol) in THF (10 mL) and H₂O (0.5 mL) was added pyrrolidine (0.95 mL, 11.4 mmol) and the solution was stirred for 2 hours. The 10 solution was concentrated in vacuo and the residue was dissolved into ethyl acetate. Concentration in vacuo provided the pyrrolidine compound as a white foam (930 mg, 93 %).

Part B: To a solution of the pyrrolidine 15 compound of part A (930 mg, 1.9 mmol) in THF (10 mL) was added potassium trimethylsilanolate (300 mg, 2.3 mmol) and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo to provide the potassium salt 20 of the acid as a white foam (1.03 g, quantitative yield).

Part C: To a solution of the acid salt of part B (1.02 g, 2.0 mmol) in dichloromethane (10 mL) cooled to zero degrees Celsius was added 4-25 methylmorpholine (0.61 mL, 6.0 mmol), O-tetrahydropyranyl hydroxylamine (240 mg, 2.04 mmol) and PyBroP® (1.03 g, 2.2 mmol) and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo. Chromatography

-157-

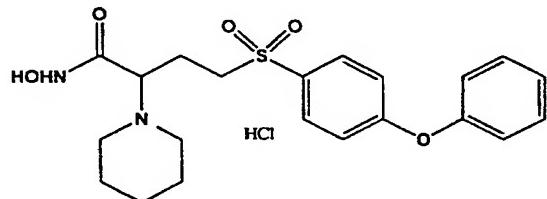
(on silica, ethyl acetate/THF) followed by tritration with ethyl ether provided the ester as a white foam (250 mg, 22%).

Part D: A solution of the ester of part C (250 mg, 0.44 mmol) in 4M HCl in dioxane (1 mL) and methanol (0.5 mL) was stirred for 30 minutes. The solution was concentrated *in vacuo* to provide the title compound as a white solid (250 mg, quantitative yield). [Data to follow on 2/26]

10

Example 15: N-hydroxy-a-[2-[(4-phenoxyphenyl)sulfonyl]-ethyl]-1-piperidineacetamide monohydrochloride

15



Part A: A solution of α -bromo- γ -lactone (10.13 g, 61.4 mmol) in pyridine (15.2 mL, 153 mmol) was 20 stirred at ambient temperature for 2 days. To this solution was added dichloromethane (50 mL) followed by NaOH (2.46 g, 61.4 mmol) in H_2O (20 mL). The solution was extracted with dichloromethane and washed with saturated NaCl and dried over $MgSO_4$. 25 Vacuum distillation provided the pyridyl lactone as a yellow oil (7.093 g, 68%).

Part B: To a slurry of NaH (60% suspension in mineral oil) in DMF (44 mL) cooled to 0° C was added 4-(phenoxy)benzenethiol (5.87 g, 29.0 mmol). After

-158-

15 minutes the pyridyl lactone of part A (3.78 g, 22.3 mmol) was added and the solution was heated to eighty-seven degrees Celsius for 16 hours. The solution was concentrated *in vacuo* and the residue 5 was partitioned between 2N HCl and ethyl ether and the aqueous was extracted with ethyl ether. The aqueous layer was concentrated *in vacuo* and the resulting oil crystallized upon standing to provide the sulfide hydrochloride salt as a white solid (4.07 10 g, 45 %).

Part C: To a solution of the sulfide of part B (1.206 g, 2.96 mmol) in DMF (10 mL) was added 4-methylmorpholine (1.30 mL, 11.8 g), N-hydroxybenzotriazole (480 mg, 3.55 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide 15 hydrochloride (737 mg, 3.84 mmol) and O-tetrahydropyranyl hydroxylamine (485 g, 4.14 mmol) and the solution stirred for 18 hours at ambient temperature. The solution was concentrated *in vacuo* 20 and the residue was partitioned between dichloromethane and H₂O. The organic layer was washed with H₂O and saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, methanol (NH₃)/dichloromethane) provided the ester as a 25 colorless oil (1.08 g, 77 %). MS(CI) MH⁺ calculated for C₂₆H₃₄N₂O₄S: 471, found 471. Analytical calculation for C₂₆H₃₄N₂O₄S: C, 66.35; H, 7.28; N, 5.95; S, 6.81. Found: C, 65.97; H, 7.51; N, 5.98; S, 6.91.

Part D: To a solution of the ester of part C 30 (234 mg, 0.50 mmol) in dichloromethane (3 mL) was added p-toluenesulfonic acid (95 mg, 0.50 mmol) followed by 3-chloroperbenzoic acid (57-86 %, 257 mg, 1.50 mmol) and the solution stirred for 1.5 hours at

-159-

ambient temperature. The solution was diluted with dichloromethane and washed with 10 % Na_2CO_3 , saturated NaHCO_3 , H_2O and saturated NaCl and dried over Na_2SO_4 . Chromatography (on silica,

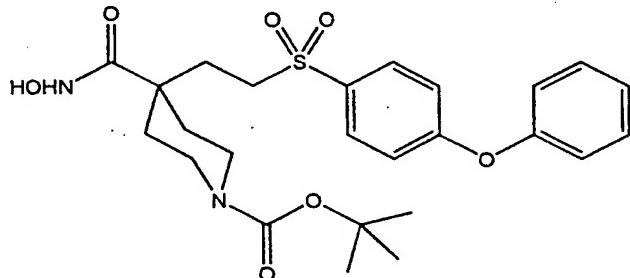
5 methanol (NH_3)/dichloromethane) provided the sulfone as a colorless oil (101 mg, 40 %). MS(CI) MH^+ calculated for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_6\text{S}$: 503, found 503.

Part E: To a solution of the sulfone of part D (100 mg, 0.20 mmol) in methanol (2 mL) was added 10 acetyl chloride (0.038 mL, 0.60 mmol) and the solution was stirred for 17 hours at ambient temperature. The solution was concentrated and the residue was diluted in ethyl acetate. The resulting precipitate was washed with ethyl acetate to provide 15 the title compound as a white solid (62 mg, 69 %). MS(CI) MH^+ calculated for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$: 419, found 419. Analytical calculation for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_5\text{S} \cdot \text{HCl}$: C, 55.44; H, 5.98; N, 6.16; Cl, 7.79. Found: C, 55.60; H, 6.24; N, 6.03; Cl, 7.65.

20

Example 16: 1,1-dimethylethyl ester 4-[
[(hydroxyamino)-carbonyl]-4-[2-[(4-
phenoxyphenyl)sulfonyl]-ethyl]-1-
piperidinecarboxylic acid

25



-160-

Part A: To a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in tetrahydrofuran (100 mL) was added a solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in THF (5 mL) dropwise over 20 minutes.

5 The solution stirred overnight at ambient temperature and concentrated in vacuo to yield a light oil. The oil was filtered through silica gel (7:3 ethyl acetate/hexane) and concentrated in vacuo to give the BOC-piperidine compound (26.2 g, quantitative yield)

10 as a clear, colorless oil.

Part B: To a solution of the BOC-piperidine of part A (5.14 g, 20.0 mmol) in THF (60 mL) cooled to -50° C was added lithium diisopropyl amide (1.8M in THF, 11.1 mL, 20.0 mmol). The solution stirred for 1 hour followed by the addition of 1-bromo-2-chloroethane (1.66 mL, 20.0 mmol). After stirring at -40° C for 15 minutes, the solution returned to ambient temperature for 4 hours. The reaction was quenched with H₂O and extracted with ethyl acetate and the organic layer was washed with H₂O and satd. NaCl, and dried over MgSO₄. Concentration in vacuo provided the chlorinated compound as a yellow oil (5.98 g, 93%).

Part C: To a cooled (0° C) suspension of sodium hydride (120 mg as a 60% dispersion in mineral oil, 3.0 mmol) in DMF (4 mL) was added 4-(phenoxy)benzenethiol (607 mg, 3.0 mmol) in DMF (2 mL) and the solution stirred for 15 minutes. To this solution was added the chlorinated compound of part A (960 mg, 3.0 mmol) in DMF (5 mL) and the solution stirred at ambient temperature for 4 hours. The solution was partitioned between ethyl acetate and H₂O and the organic was washed with 15% KHSO₄ and satd.

-161-

NaCl and dried over MgSO₄. Chromatography (1:9 ethyl acetate/hexane) provided the sulfide as an oil (1.26 g, 87%).

Part D: To a solution of the sulfide of Part C (1.25 g, 2.6 mmol) in dichloromethane (20 mL) cooled to 0° C, was added 3-chloroperbenzoic acid (80%, 1.11 g, 5.1 mmol). The solution stirred at ambient temperature for 2.5 hours. Additional dichloromethane was added and the organic layer was washed with H₂O, satd. NaHCO₃, and satd. NaCl and dried over MgSO₄. Chromatography (20 ethyl acetate/80 hexane) provided the sulfone as a solid (740 mg, 56%). MS(CI) MH⁺ calcd. for C₂₇H₃₅NO₇S: 518, found 518. HRMS calcd. for C₂₇H₃₅NO₇S: 518.2212, found 518.2222.

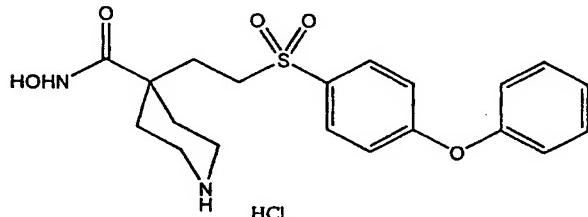
Part E: To a solution of the sulfone of Part D (708 mg, 1.37 mmol) in THF (5 mL) and ethanol (5 mL) was added sodium hydroxide (547 mg, 13.7 mmol) in H₂O (7 mL). The solution was heated to 65° C for 18 hours. The solution was concentrated in vacuo and the residue was suspended in H₂O and acidified with 2N HCl. The solution was extracted with ethyl acetate and the organic layer was washed with sat. NaCl and dried over MgSO₄. Concentration in vacuo provided the acid as a light yellow foam (500 mg, 75%). MS(CI) MH⁺ calcd. for C₂₅H₃₁NO₇S: , found . HRMS calcd. for C₂₅H₃₁NO₇S: , found . Anal. calcd. for C₂₅H₃₁NO₇S 0.3H₂O: C, 60.66; H, 6.43; N, 2.83; S, 6.48. Found: C, 60.20; H, 6.59; N, 2.63; S, 5.85.

Part F: To a solution of the acid of part E (475 mg, 0.97 mmol) in DMF (10 mL) was added N-hydroxybenzotriazole•H₂O (157 mg, 1.16 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (260 mg, 1.36 mmol). After 5 minutes of

-162-

stirring at ambient temperature 4-methylmorpholine (0.32 mL, 2.91 mmol) was added followed by 50% aqueous NH₂OH (0.192 mL, 2.91 mmol). The solution stirred for 7 hours. Additional N-5 hydroxybenzotriazole•H₂O (157 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (260 mg), 4-methylmorpholine (0.32 mL) and 50% aqueous NH₂OH were added and the solution stirred for 48 hours. The solution was diluted with H₂O, extracted with ethyl acetate and washed with satd. NaCl and dried over MgSO₄. Reverse phase HPLC (acetonitrile/H₂O) provided the title compound as a white solid (228 mg, 47%). HPLC purity: >99%. MS(CI) MH⁺ calcd. for C₂₅H₃₂N₂O₇S: 505, found 505. Anal. calcd. for C₂₅H₃₂N₂O₇S•0.25H₂O: C, 58.98; H, 6.43; N, 5.50. Found: C, 58.87; H, 6.40; N, 5.38.

Example 17: N-hydroxy-4-[2-[(4-phenoxyphenyl)sulfonyl]-ethyl]-4-piperidine carboxamide monohydrochloride



Part A: To a solution of ethyl isonipeotate (15.7 g, 0.1 mol) in tetrahydrofuran (100 mL) was added a solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in THF (5 mL) dropwise over 20 minutes. The solution stirred overnight at ambient temperature and concentrated *in vacuo* to yield a light oil. The

-163-

oil was filtered through silica gel (7:3 ethyl acetate/hexane) and concentrated in vacuo to give the BOC-piperidine compound (26.2 g, quantitative yield) as a clear, colorless oil.

5 Part B: To a solution of the BOC-piperidine of part A (5.14 g, 20.0 mmol) in THF (60 mL) cooled to -50° C was added lithium diisopropyl amide (1.8M in THF, 11.1 mL, 20.0 mmol). The solution stirred for 1 hour followed by the addition of 1-bromo-2-chloroethane (1.66 mL, 20.0 mmol). After stirring at 10 -40° C for 15 minutes, the solution returned to ambient temperature for 4 hours. The reaction was quenched with H₂O and extracted with ethyl acetate and the organic layer was washed with H₂O and satd. NaCl, 15 and dried over MgSO₄. Concentration in vacuo provided the chlorinated compound as a yellow oil (5.98 g, 93%).

Part C: To a cooled (0° C) suspension of sodium hydride (120 mg as a 60% dispersion in mineral oil, 20 3.0 mmol) in DMF (4 mL) was added 4-(phenoxy)benzene (607 mg, 3.0 mmol) in DMF (2 mL) and the solution stirred for 15 minutes. To this solution was added the chlorinated compound of part A (960 mg, 3.0 mmol) in DMF (5 mL) and the solution stirred at ambient 25 temperature for 4 hours. The solution was partitioned between ethyl acetate and H₂O and the organic was washed with 15% KHSO₄ and satd. NaCl and dried over MgSO₄. Chromatography (1:9 ethyl acetate/hexane) provided the sulfide as an oil (1.26 30 g, 87%).

Part D: To a solution of the sulfide of Part C (1.25 g, 2.6 mmol) in dichloromethane (20 mL) cooled to 0° C, was added 3-chloroperbenzoic acid (80%, 1.11

-164-

g, 5.1 mmol). The solution stirred at ambient temperature for 2.5 hours. Additional dichloromethane was added and the organic layer was washed with H₂O, satd. NaHCO₃, and satd. NaCl and dried over MgSO₄. Chromatography (20 ethyl acetate/80 hexane) provided the sulfone as a solid (740 mg, 56%). HRMS calcd. for C₂₇H₃₅NO₂S: 518.2212, found 518.2222.

Part E: To a solution of the sulfone of Part D (708 mg, 1.37 mmol) in THF (5 mL) and ethanol (5 mL) was added sodium hydroxide (547 mg, 13.7 mmol) in H₂O (7 mL). The solution was heated to 65° C for 18 hours. The solution was concentrated *in vacuo* and the residue was suspended in H₂O and acidified with 2N HCl. The solution was extracted with ethyl acetate and the organic layer was washed with satd. NaCl and dried over MgSO₄. Concentration *in vacuo* provided the acid as a light yellow foam (500 mg, 75%). Anal. calcd. for C₂₅H₃₁NO₂S•0.3H₂O: C, 60.64; H, 6.43; N, 2.83; S, 6.48. Found: C, 60.20; H, 6.59; N, 2.63; S, 5.85.

Part F: To a solution of the acid of part E (475 mg, 0.97 mmol) in DMF (10 mL) was added N-hydroxybenzotriazole•H₂O (157 mg, 1.16 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (260 mg, 1.36 mmol). After 5 minutes of stirring at ambient temperature 4-methylmorpholine (0.32 mL, 2.91 mmol) was added followed by 50% aqueous NH₂OH (0.192 mL, 2.91 mmol). The solution stirred for 7 hours. Additional N-hydroxybenzotriazole•H₂O (157 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (260 mg), 4-methylmorpholine (0.32 mL)

-165-

and 50% aqueous NH₂OH were added and the solution stirred for 48 hours. The solution was diluted with H₂O, extracted with ethyl acetate and washed with satd. NaCl and dried over MgSO₄. Reverse phase HPLC (acetonitrile/H₂O) provided the hydroxamate as a white solid (228 mg, 47%). Anal. calcd. for C₂₅H₃₂N₂O₅S•0.25H₂O: C, 58.98; H, 6.43; N, 5.50. Found: C, 58.87; H, 6.40; N, 5.38.

Part G: To a cooled (0° C) solution of the BOC-hydroxamate of Part F (205 mg, 0.41 mmol) was bubbled HCl gas for 5 minutes followed by standing for 1 hour. Concentration followed by trituration with ethyl ether provided the title compound as a white solid (183 mg, quantitative yield). MS(CI) MH⁺ calcd. for C₂₀H₂₄N₂O₅S: 405, found 405. HRMS calcd. for C₂₀H₂₄N₂O₅S: 405.1484, found 405.1484. Anal. calcd. for C₂₀H₂₄N₂O₅S HCl H₂O: C, 52.34; H, 5.97; N, 6.10; Cl, 7.72. Found: C, 52.07; H, 5.97; N, 5.85; Cl, 8.04.

Example 18: In Vitro Metalloprotease Inhibition

Several of the compounds prepared in the manner described in Examples 1 to 17 were assayed for activity by an *in vitro* assay. Following the procedures of Knight et al., *FEBS Lett.* **296(3)**:263 (1992). Briefly, 4-aminophenylmercuric acetate (APMA) or trypsin activated MMPs were incubated with various concentrations of the inhibitor compound at room temperature for 5 minutes.

More specifically, recombinant human MMP-13 and MMP-1 enzymes were prepared in laboratories of the assignee. MMP-13 was expressed in baculovirus as a proenzyme, and purified first over a heparin agarose column and then over a chelating zinc

-166-

chloride column. The proenzyme was activated by APMA for use in the assay. MMP-1 expressed in transfected HT-1080 cells was provided by Dr. Howard Welgus of Washington University, St. Louis, MO. The enzyme was 5 also activated using APMA and was then purified over a hydroxamic acid column.

The enzyme substrate is a methoxycoumarin-containing polypeptide having the following sequence:

MCA-ProLeuGlyLeuDpaAlaArgNH², wherein MCA is 10 methoxycoumarin and Dpa is 3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl alanine. This substrate is commercially available from Baychem as product M-1895.

The buffer used for assays contained 100 mM 15 Tris-HCl, 100 mM NaCl, 10 mM CaCl₂ and 0.05 percent polyethyleneglycol (23) lauryl ether at a pH value of 7.5. Assays were carried out at room temperature, and dimethyl sulfoxide (DMSO) at a final concentration of 1 percent was used to dissolve 20 inhibitor compound.

The assayed inhibitor compound in DMSO/buffer solution was compared to an equal amount of DMSO/buffer with no inhibitor as control using Microfluor™ White Plates (Dynatech). The inhibitor 25 or control solution was maintained in the plate for 10 minutes and the substrate was added to provide a final concentration of 4 µM.

In the absence of inhibitor activity, a fluorogenic peptide was cleaved at the gly-leu 30 peptide bond, separating the highly fluorogenic peptide from a 2,4-dinitrophenyl quencher, resulting in an increase of fluorescence intensity (excitation at 328 nm/emission at 415 nm). Inhibition was

-167-

measured as a reduction in fluorescent intensity as a function of inhibitor concentration, using a Perkin Elmer L550 plate reader. The IC₅₀ values were calculated from those values. The results are set forth in the Inhibition Table below, reported in terms of IC₅₀ to three significant figures.

-168-

Table 37
Inhibition Table
(IC₅₀ values in nM)

5

<u>Example</u>	<u>MMP -13</u>	<u>MMP-1</u>	<u>MMP-2</u>
1	1.9	6300	0.3
2	8.8	>10,000	2.0
3	2600	>10,000	1000
4	54.4	>10,000	15.8
5	1.8	>10,000	3.2
6	2000		
7	400	>10,000	120
8a	5.0	>10,000	2.2
9a	3.0	7000	1.3
10	2.4	10,000	1.5
11	<0.1	50	<0.1
12	1.6	3300	0.3
13	1.4	770	0.3
13a	1.8	1800	0.6
14	2.4	>10,000	1.8
15	13.9	>10,000	7.7
16	400	>10,000	169
17	169	>10,000	70

Example 19: In Vivo Angiogenesis Assay

The study of angiogenesis depends on a
 10 reliable and reproducible model for the stimulation
 and inhibition of a neovascular response. The
 corneal micropocket assay provides such a model of

-169-

angiogenesis in the cornea of a mouse. See, *A Model of Angiogenesis in the Mouse Cornea*; Kenyon, BM, et al., *Investigative Ophthalmology & Visual Science*, July 1996, Vol. 37, No. 8.

5 In this assay, uniformly sized Hydron™ pellets containing bFGF and sucralfate are prepared and surgically implanted into the stroma mouse cornea adjacent to the temporal limbus. The pellets are formed by making a suspension of 20 µL sterile saline
10 containing 10 µg recombinant bFGF, 10 mg of sucralfate and 10 µL of 12 percent Hydron™ in ethanol. The slurry is then deposited on a 10 x 10 mm piece of sterile nylon mesh. After drying, the nylon fibers of the mesh are separated to release the
15 pellets.

The corneal pocket is made by anesthetizing a 7 week old C57Bl/6 female mouse, then proptosing the eye with a jeweler's forceps. Using a dissecting microscope, a central, intrastromal linear keratotomy 20 of approximately 0.6 mm in length is performed with a #15 surgical blade, parallel to the insertion of the lateral rectus muscle. Using a modified cataract knife, a lamellar micropocket is dissected toward the temporal limbus. The pocket is extended to within 1.0 mm of the temporal limbus. A single pellet is placed 25 on the corneal surface at the base of the pocket with a jeweler's forceps. The pellet is then advanced to the temporal end of the pocket. Antibiotic ointment is then applied to the eye.

30 Mice are dosed on a daily basis for the duration of the assay. Dosing of the animals is based on bioavailability and overall potency of the compound. an exemplary dose is 50 mg/kg bid, po.

-170-

Neovascularization of the corneal stroma begins at about day three and is permitted to continue under the influence of the assayed compound until day five. At day five, the degree of angiogenic inhibition is 5 scored by viewing the neovascular progression with a slit lamp microscope.

The mice are anesthetized and the studied eye is once again proptosed. The maximum vessel length of neovascularization, extending from the 10 limbal vascular plexus toward the pellet is measured. In addition, the contiguous circumferential zone of neovascularization is measured as clock hours, where 30 degrees of arc equals one clock hour. The area of angiogenesis is calculated as follows.

15

$$\text{area} = \frac{(0.4 \times \text{clock hours} \times 3.14 \times \text{vessel length (in mm)})}{2}$$

The studied mice are thereafter compared to control mice and the difference in the area of 20 neovascularization is recorded. A contemplated compound typically exhibits about 25 to about 75 percent inhibition, whereas the vehicle control exhibits zero percent inhibition.

25 From the foregoing, it will be observed that numerous modifications and variations can be effectuated without departing from the true spirit and scope of the novel concepts of the present invention. It is to be understood that no limitation 30 with respect to the specific example presented is intended or should be inferred. The disclosure is

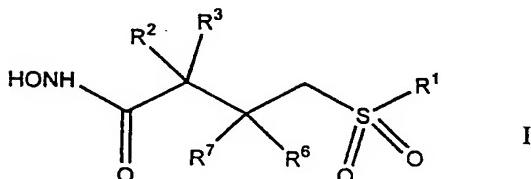
-171-

intended to cover by the appended claims all such modifications as fall within the scope of the claims.

-172-

WHAT IS CLAIMED IS:

1. A compound corresponding to Formula I:



5 wherein

- R¹ is a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted 10 SO₂-group and having a length greater than about that of a hexyl group and less than about that of an eicosyl group, said R¹ defining a three-dimensional volume, when rotated about an axis drawn through the SO₂-bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the SO₂-bonded 15 1-position and the center of 3,4-bond of a 5-membered ring radical, whose widest dimension in a direction transverse to the axis of rotation is about that of one furanyl ring to about that of two phenyl rings;
- R² and R³ are independently selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, hydroxy-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy-C₁-C₄ hydrocarbyl, aryloxy-C₁-C₄ hydrocarbyl, amino-C₁-C₄ 20 hydrocarbyl, C₁-C₄ hydrocarbylthio-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylsulfonyl-C₁-C₄ hydrocarbyl, 25 aminosulfonylamino-C₁-C₄ hydrocarbyl,

-173-

- aminocarbonylamino- C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylcarbonylamino-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl and benzylxy-C₁-C₄ hydrocarbyl, but only one of R² and 5 R³ is other than hydrido or C₁-C₄ hydrocarbyl; or R² and R³ together with the depicted carbon atom to which they are bonded form a heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally 10 substituted with one or two oxygens when sulfur and being substituted with a moiety R⁵ that is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl 15 group when nitrogen; and R⁶ and R⁷ are independently selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, hydroxy-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy-C₁-C₄ 20 hydrocarbyl, aryloxy-C₁-C₄ hydrocarbyl, amino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylthio-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylsulfonyl-C₁-C₄ hydrocarbyl, aminosulfonylamino-C₁-C₄ hydrocarbyl, 25 aminocarbonylamino- C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylcarbonylamino-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl and benzylxy-C₁-C₄ hydrocarbyl, but only one of R⁶ and R⁷ is other than hydrido or C₁-C₄ hydrocarbyl; or

-174-

R⁶ and R⁷ together with the depicted carbon atom to which they are bonded form a heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally
5 substituted with one or two oxygens when sulfur and being substituted with a moiety R⁵ that is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl
10 group when nitrogen;

only one of R², R³, R⁶ and R⁷ is other than hydrido, C₁-C₄ hydrocarbyl or forms part of a heterocyclic ring structure as recited.

15 2. The compound according to claim 1 wherein said 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical of R¹ is substituted with a substituent, R⁴, that has a chain length of 3 to about 14 carbon atoms.

20 3. The compound according to claim 2 wherein said R⁴ substituent is selected from the group consisting of a phenyl group, a phenoxy group, a thiophenoxy group, an anilino group, a phenylazo
25 group, a phenylureido, a benzamido], a nicotinamido, an isonicotinamido, a picolinamido group, a heterocyclo, heterocyclohydrocarbyl, arylheterocyclohydrocarbyl, arylhydrocarbyl, heteroarylhydrocarbyl,
30 heteroarylheterocyclohydrocarbyl, arylhydrocarbyloxyhydrocarbyl, aryloxyhydrocarbyl, hydrocarboylhydrocarbyl, arylhydrocarboylhydrocarbyl,

-175-

arylcarbonylhydrocarbyl, arylazoaryl,
arylhydrazinoaryl, hydrocarbylthiohydrocarbyl,
hydrocarbylthioaryl, arylthiohydrocarbyl,
heteroarylthiohydrocarbyl,
5 hydrocarbylthioarylhydrocarbyl,
arylhydrocarbylthiohydrocarbyl
arylhydrocarbylthioaryl, arylhydrocarbylamino,
heteroarylhydrocarbylamino, and a heteroarylthio
group.

10

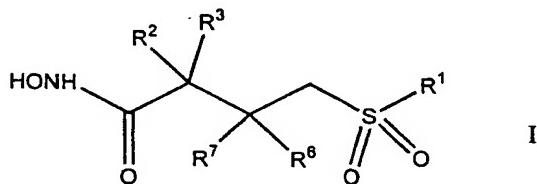
4. The compound according to claim 3
wherein said R⁴ substituent is itself substituted by
one or more substituents selected from the group
consisting of a halogen, hydrocarbyl, hydrocarbyloxy,
15 nitro, cyano, perfluorohydrocarbyl,
trifluoromethylhydrocarbyl, hydroxy, mercapto,
hydroxycarbonyl, aryloxy, arylthio, arylamino,
arylhydrocarbyl, aryl, heteroaryloxy, heteroarylthio,
heteroarylamino, heteroarylhydrocarbyl,
20 hydrocarbyloxcarbonylhydrocarbyl, heterocyclooxy,
hydroxycarbonylhydrocarbyl, heterocyclthio,
heterocycloamino, cyclohydrocarbyloxy,
cyclohydrocarbylthio, cyclohydrocarbylamino,
heteroarylhydrocarbyloxy, heteroarylhydrocarbylthio,
25 heteroarylhydrocarbylamino, arylhydrocarbyloxy,
arylhydrocarbylthio, arylhydrocarbylamino,
heterocyclic, heteroaryl, hydroxycarbonyl-
hydrocarbyloxy, alkoxy carbonylalkoxy, hydrocarbyloyl,
arylcarbonyl, arylhydrocarbyloyl, hydrocarboyoxy,
30 arylhydrocarboyoxy, hydroxyhydrocarbyl,
hydroxyhydrocarbyloxy, hydrocarbylthio,
hydrocarbyloxyhydrocarbylthio,
hydrocarbyloxy carbonyl,

-176-

- hydroxycarbonylhydrocarbyloxy, hydrocarbyloxy-
 carbonylhydrocarbyl, hydrocarbylhydroxycarbonyl-
 hydrocarbylthio,
 hydrocarbyloxycarbonylhydrocarbyloxy,
 5 hydrocarbyloxycarbonylhydrocarbylthio, amino,
 hydrocarbylcarbonylamino, arylcarbonylamino,
 cyclohydrocarbylcarbonylamino,
 heterocyclohydrocarbylcarbonylamino,
 arylhydrocarbylcarbonylamino,
 10 heteroarylcarbonylamino,
 heteroarylhydrocarbylcarbonylamino,
 heterocyclohydrocarbyloxy, hydrocarbysulfonylamino,
 arylsulfonylamino, arylhydrocarbysulfonylamino,
 heteroarylsulfonylamino, heteroarylhydrocarbyl-
 15 sulfonylamino, cyclohydrocarbysulfonylamino,
 heterocyclohydrocarbysulfonylamino and N-
 monosubstituted or N,N-disubstituted aminohydrocarbyl
 group, wherein the substituent(s) on the nitrogen are
 selected from the group consisting of hydrocarbyl,
 20 aryl, arylhydrocarbyl, cyclohydrocarbyl,
 arylhydrocarbyloxycarbonyl, hydrocarbyloxycarbonyl,
 and hydrocarboyl, or wherein the nitrogen and two
 substituents attached thereto form a 5- to 8-membered
 heterocyclic or heteroaryl ring group.

25

5. A compound corresponding to Formula I:



-177-

wherein

R¹ is a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or 5 heteroaryl radical bonded directly to the depicted SO₂-group that is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent R⁴ selected from the group consisting of one other 10 single-ringed cyclohydrocarbyl, heterocyclo, aryl or heteroaryl group, a C₃-C₁₄ hydrocarbyl group, a C₂-C₁₄ hydrocarbyloxy group, a phenoxy group, a thiophenoxy group, a 4-thiopyridyl group, a phenylazo group, a phenylureido group, a nicotinamido group, an 15 isonicotinamido group, a picolinamido group, an anilino group and a benzamido group;

R² is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, N-piperidinyl, N-piperazinyl, N-(C₁-C₄ hydrocarbyl)piperazinyl, N-pyrrolidinyl, N-morpholinyl and -Y-Z group, wherein 20 Y is -O or -NR¹¹, wherein R¹¹ is hydrido or C₁-C₄ hydrocarbyl, and -Z is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, benzoyl, (2-pyridinyl)methyl, (3-pyridinyl)methyl or (4-pyridinyl)methyl, 2-(morpholinyl)ethyl, 2-(piperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(N-methylpiperazinyl)ethyl, 2-(thiomorpholinyl)ethyl, 2-(thiomorpholinyl sulfone)ethyl, 2-(succinimidyl)ethyl, 2-(hydantoinyl), 2-(3-methylhydantoinyl)ethyl, 2-(N-C₁-C₄ hydrocarbylamino)ethyl, 2-[N,N-di(C₁-C₄

-178-

hydrocarbyl)amino]ethyl, carboxy C₁-C₄ hydrocarbyl, piperidinyl, 2-, 3-, or 4-pyridinyl, sulfonamido, C₁-C₄ hydrocarbysulfonyl, C₁-C₄ hydrocarbylphosphonyl and C(O)-W wherein -W is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy -CHR¹²NH₂ wherein R¹² is the side chain of a D or L amino acid, benzyloxy, benzylamino and amino group;

R³ is a hydrido or C₁-C₄ hydrocarbyl group;
10 or

R² and R³ together with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being optionally substituted with a moiety selected from the group consisting of a C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen; and

R⁶ is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, N-piperidinyl, N-piperazinyl, N-(C₁-C₄ hydrocarbyl)piperazinyl, N-pyrrolidinyl, N-morpholinyl and -Y-Z group, wherein -Y is -O or -NR¹¹, wherein R¹¹ is hydrido or C₁-C₄ hydrocarbyl, and -Z is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, benzoyl, (2-pyridinyl)methyl, (3-pyridinyl)methyl or (4-pyridinyl)methyl, 2-(morpholinyl)ethyl, 2-(piperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(N-methylpiperazinyl)ethyl, 2-(thiomorpholinyl)ethyl, 2-

-179-

(thiomorpholinyl sulfone)ethyl, 2-(succinimidyl)ethyl, 2-(hydantoinyl), 2-(3-methylhydantoinyl)ethyl, 2-(N-C₁-C₄ hydrocarbylamino)ethyl, 2-[N,N-di(C₁-C₄ hydrocarbyl)amino]ethyl, carboxy C₁-C₄ hydrocarbyl, piperidinyl, 2-, 3-, or 4-pyridinyl, sulfonamido, C₁-C₄ hydrocarbysulfonyl, C₁-C₄ hydrocarbylphosphonyl and C(O)-W wherein -W is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy -CHR¹²NH₂ wherein R¹² is the side chain of a D or L amino acid, benzyloxy, benzylamino and amino group;

R⁷ is a hydrido or C₁-C₄ hydrocarbyl group;

or

R⁶ and R⁷ together with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being optionally substituted with a moiety selected from the group consisting of a C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen;

only one of R², R³, R⁶ and R⁷ is other than hydrido, C₁-C₄ hydrocarbyl or forms part of a heterocyclic ring structure as recited.

6. The compound according to claim 5 wherein said R¹ substituent is PhR⁴ in which Ph is phenyl substituted with R⁴ at the 4-position, and

-180-

said R⁴ is a phenyl, phenoxy, thiophenoxy, phenylazo, benzamido, anilino, nicotinamido, isonicotinamido, picolinamido or phenylureido group that is optionally substituted at the meta- or para-position or both

5 with a moiety that is selected from the group consisting of a halogen, a C₁-C₉ hydrocarbyloxy group, a C₁-C₁₀ hydrocarbyl group, a di- C₁-C₉ hydrocarbylamino group, a carboxyl C₁-C₈ hydrocarbyl group, a C₁-C₄ hydrocarbyloxy carbonyl C₁-C₄

10 hydrocarbyl group, a C₁-C₄ hydrocarbyloxycarbonyl C₁-C₄ hydrocarbyl group and a carboxamido C₁-C₈ hydrocarbyl group, or is substituted at the meta- and para-positions by two methyl groups or by a methylenedioxy group.

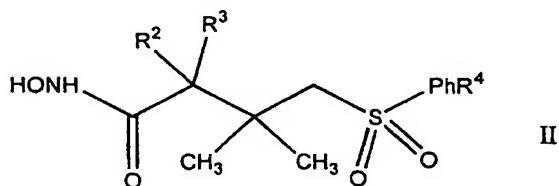
15

7. The compound according to claim 5
wherein R⁶ and R⁷ are both hydrido.

20 8. The compound according to claim 5
wherein R⁶ and R⁷ are both methyl.

25 9. The compound according to claim 5
wherein said R¹ substituent has a length greater than
that of an octyl group and less than that of a
stearyl group.

10. A compound corresponding to Formula



-181-

II:

wherein Ph is a phenyl radical bonded directly to the depicted SO₂-group that is itself
5 substituted at its own 4-position with a substituent R⁴ selected from the group consisting of one other single-ringed aryl or heteroaryl group, a C₃-C₁₄ hydrocarbyl group, a C₂-C₁₄ hydrocarbyloxy group, a phenoxy group, a thiophenoxy group, a 4-thiopyridyl group, a phenylazo group, a phenylureido group, a 10 nicotinamido group, an isonicotinamido group, a picolinamido group, an anilino group and a benzamido group;

R² is selected from the group consisting of
15 a hydrido, C₁-C₄ hydrocarbyl, N-piperidinyl, N-piperazinyl, N-(C₁-C₄ hydrocarbyl)piperazinyl, N-pyrrolidinyl, N-morpholinyl and -Y-Z group, wherein -Y is -O or -NR¹¹, wherein R¹¹ is hydrido or C₁-C₄ hydrocarbyl, and -Z is selected from the group
20 consisting of a hydrido, C₁-C₄ hydrocarbyl, benzoyl, (2-pyridinyl)methyl, (3-pyridinyl)methyl or (4-pyridinyl)methyl, 2-(morpholinyl)ethyl, 2-(piperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(N-methylpiperazinyl)ethyl, 2-(thiomorpholinyl)ethyl, 25 (thiomorpholinyl sulfone)ethyl, 2-(succinimidyl)ethyl, 2-(hydantoinyl), 2-(3-methylhydantoinyl)ethyl, 2-(N-C₁-C₄ hydrocarbylamino)ethyl, 2-[N,N-di(C₁-C₄ hydrocarbyl)amino]ethyl, carboxy C₁-C₄ hydrocarbyl,
30 piperidinyl, 2-, 3-, or 4-pyridinyl, sulfonamido, C₁-C₄ hydrocarbylsulfonyl, C₁-C₄ hydrocarbylphosphonyl

-182-

and C(O)-W wherein -W is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy -CHR¹²NH₂ wherein R¹² is the side chain of a D or L amino acid, benzyloxy, benzylamino and amino group;

5 R³ is a hydrido or C₁-C₄ hydrocarbyl group;
or

10 R² and R³ together with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being substituted with a moiety R⁵ that is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen.

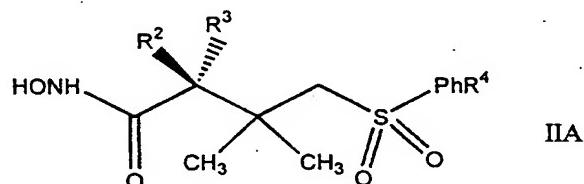
11. The compound according to claim 10
20 wherein said R⁴ is a phenyl, phenoxy, anilino, thiophenoxy, benzamido, nicotinamido, isonicotinamido, picolinamido or phenylureido group that is itself optionally substituted at meta or para position or both with a moiety that is selected from
25 the group consisting of a halogen, a C₁-C₉ hydrocarbyloxy group, a C₁-C₁₀ hydrocarbyl group, a di-C₁-C₉ hydrocarbylamino group, a carboxyl C₁-C₈ hydrocarbyl group, a C₁-C₄ hydrocarbyloxy carbonyl C₁-C₄ hydrocarbyl group, a C₁-C₄ hydrocarbyloxy carbonyl C₁-C₄ hydrocarbyl group, and a

-183-

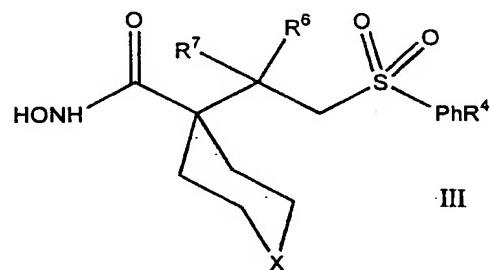
carboxamido C₁-C₈ hydrocarbyl group, or is substituted at the meta- and para-positions by two methyl groups or by a C₁-C₂ alkylenedioxy group.

5 12. The compound according to claim 11 wherein said R⁴ is a phenoxy or thiophenoxy group that is unsubstituted.

10 13. The compound according to claim 10 corresponding in stereoconfiguration to Formula IIA



14. The compound according to claim 10
15. that corresponds in structure to Formula III



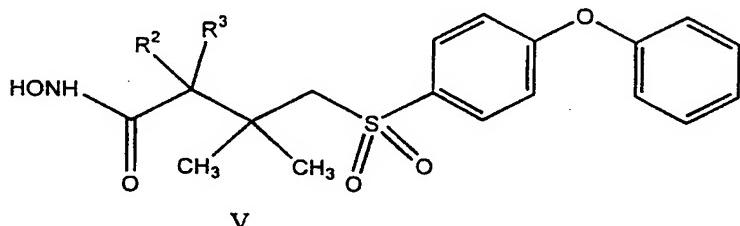
wherein X is O, S, S(O), S(O₂) or NR⁵, wherein R⁵ is
20 selected from the group consisting of a C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄

-184-

carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group, and R⁶ and R⁷ are independently a hydrido or methyl group.

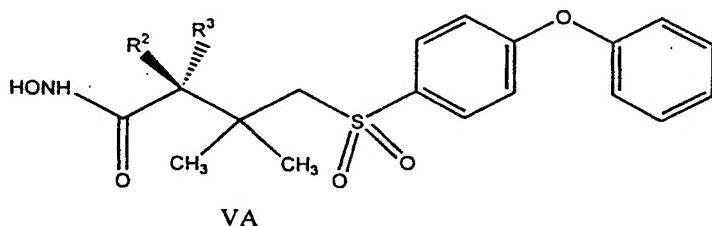
5 15. The compound according to claim 10
wherein PhR⁴ is 4-phenoxyphenyl.

16. The compound according to claim 15
corresponding in structure to Formula V



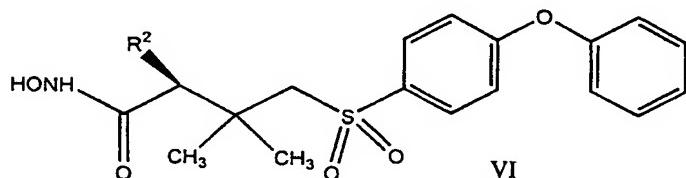
10

17. The compound according to claim 16
corresponding in stereoconfiguration to Formula VII



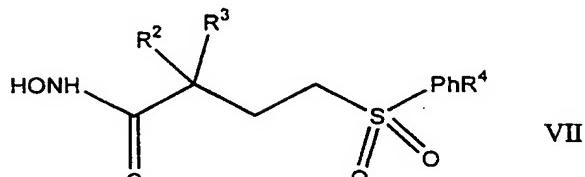
15

18. The compound according to claim 17
corresponding in stereoconfiguration to Formula VI



-185-

19. A compound corresponding to Formula
VII:



5

wherein

Ph is a phenyl radical bonded directly to
10 the depicted SO₂-group that is itself substituted at
its own 4-position with a substituent R⁴ selected
from the group consisting of one other single-ringed
aryl or heteroaryl group, a C₃-C₁₄ hydrocarbyl group,
a C₂-C₁₄ hydrocarbyloxy group, a phenoxy group, a
15 thiophenoxy group, a 4-thiopyridyl group, a phenylazo
group, a phenylureido group, a nicotinamido group, an
isonicotinamido group, a picolinamido group, an
anilino group and a benzamido group;

R² is selected from the group consisting of
20 a hydrido, C₁-C₄ hydrocarbyl, N-piperidinyl, N-
piperazinyl, N-(C₁-C₄ hydrocarbyl)piperazinyl, N-
pyrrolidinyl, N-morpholinyl and -Y-Z group, wherein -
Y is -O or -NR¹¹, wherein R¹¹ is hydrido or C₁-C₄
hydrocarbyl, and -Z is selected from the group
25 consisting of a hydrido, C₁-C₄ hydrocarbyl, benzoyl,
(2-pyridinyl)methyl, (3-pyridinyl)methyl or (4-
pyridinyl)methyl, 2-(morpholinyl)ethyl, 2-
(piperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(N-

-186-

- methyl(piperazinyl)ethyl, 2-(thiomorpholinyl)ethyl, 2-(thiomorpholinyl sulfone)ethyl, 2-(succinimidyl)ethyl, 2-(hydantoinyl), 2-(3-methylhydantoinyl)ethyl, 2-(N-C₁-C₄ hydrocarbylamino)ethyl, 2-[N,N-di(C₁-C₄ hydrocarbyl)amino]ethyl, carboxy C₁-C₄ hydrocarbyl, piperidinyl, 2-, 3-, or 4-pyridinyl, sulfonamido, C₁-C₄ hydrocarbysulfonyl, C₁-C₄ hydrocarbylphosphonyl and C(O)-W wherein -W is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy -CHR¹²NH₂ wherein R¹² is the side chain of a D or L amino acid, benzyloxy, benzylamino and amino group;
- 15 R³ is a hydrido or C₁-C₄ hydrocarbyl group;
- 15 or
- 20 R² and R³ together with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being substituted with a moiety R⁵ that is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen.

20. The compound according to claim 19 wherein said R⁴ is a phenyl, phenoxy, anilino, thiophenoxy, benzamido, nicotinamido, 30 isonicotinamido, picolinamido or phenylureido group that is itself optionally substituted at meta or para

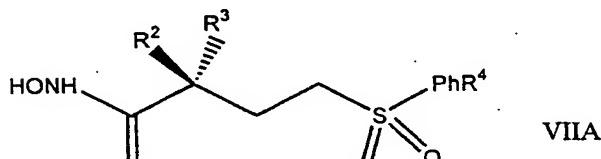
-187-

position or both with a moiety that is selected from the group consisting of a halogen, a C₁-C₉ hydrocarbyloxy group, a C₁-C₁₀ hydrocarbyl group, a di-C₁-C₉ hydrocarbylamino group, a carboxyl C₁-C₈ hydrocarbyl group, a C₁-C₄ hydrocarbyloxy carbonyl C₁-C₄ hydrocarbyl group, a C₁-C₄ hydrocarbyloxycarbonyl C₁-C₄ hydrocarbyl group, and a carboxamido C₁-C₈ hydrocarbyl group, or is substituted at the meta- and para-positions by two methyl groups or by a C₁-C₂ alkylenedioxy group.

21. The compound according to claim 20 wherein said R⁴ is a phenoxy or thiophenoxy group that is unsubstituted.

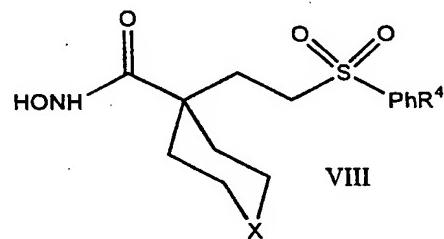
15

22. The compound according to claim 19



corresponding in stereoconfiguration to Formula VIIA

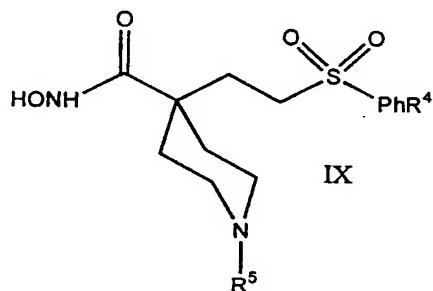
20 23. The compound according to claim 19 that corresponds in structure to Formula VIII



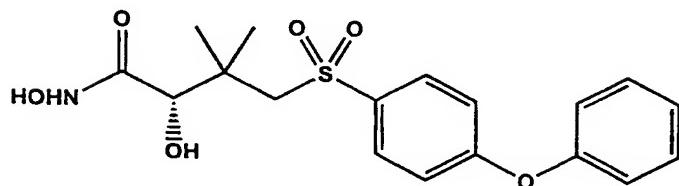
-188-

wherein X is O, S, S(O), S(O) or NR⁵, wherein R⁵ is selected from the group consisting of a C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group, and R⁶ and R⁷ are independently a hydrido or methyl group.

10 24. The compound according to claim 23 corresponding in structure to Formula IX

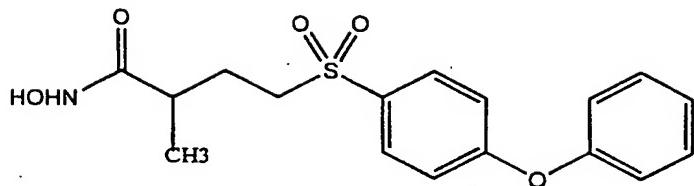


15 25. A compound corresponding to the formula



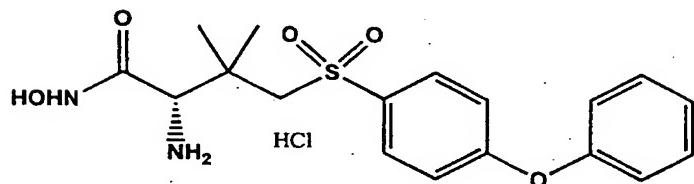
20 26. A compound corresponding to the formula

-189-

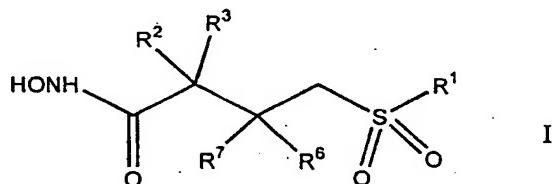


27. A compound corresponding to the formula

5



28. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity that comprises
10 administering a compound corresponding in structure to Formula I in an MMP enzyme-inhibiting effective amount to a mammalian host having such a condition:



15

wherein

R¹ is a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or
20 heteroaryl radical bonded directly to the depicted SO₂-group and having a length greater than about that

-190-

of a hexyl group and less than about that of an eicosyl group, said R¹ defining a three-dimensional volume, when rotated about an axis drawn through the SO₂-bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the SO₂-bonded 1-position and the center of 3,4-bond of a 5-membered ring radical, whose widest dimension in a direction transverse to the axis of rotation is about that of one furanyl ring to about that of two phenyl rings;

R² and R³ are independently selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, hydroxy-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy-C₁-C₄ hydrocarbyl, aryloxy-C₁-C₄ hydrocarbyl, amino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylthio-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylsulfonyl-C₁-C₄ hydrocarbyl, aminosulfonylamino-C₁-C₄ hydrocarbyl, aminocarbonylamino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylcarbonylamino-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl and benzyloxy-C₁-C₄ hydrocarbyl, but only one of R² and R³ is other than hydrido or C₁-C₄ hydrocarbyl; or

R² and R³ together with the depicted carbon atom to which they are bonded form a heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being substituted with a moiety R⁵ that is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄

-191-

carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen; and

- R⁶ and R⁷ are independently selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, hydroxy-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbyloxy-C₁-C₄ hydrocarbyl, aryloxy-C₁-C₄ hydrocarbyl, amino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylthio-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylsulfonanyl-C₁-C₄ hydrocarbyl, aminosulfonylamino-C₁-C₄ hydrocarbyl, aminocarbonylamino-C₁-C₄ hydrocarbyl, C₁-C₄ hydrocarbylcarbonylamino-C₁-C₄ hydrocarbyl, aryl-C₁-C₄ hydrocarbyl, heteroaryl-C₁-C₄ hydrocarbyl and benzyloxy-C₁-C₄ hydrocarbyl, but only one of R⁶ and R⁷ is other than hydrido or C₁-C₄ hydrocarbyl; or
- R⁶ and R⁷ together with the depicted carbon atom to which they are bonded form a heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being substituted with a moiety R⁵ that is selected from the group consisting of a hydrido, C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ carbonylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen;
- only one of R², R³, R⁶ and R⁷ is other than hydrido, C₁-C₄ hydrocarbyl or forms part of a heterocyclic ring structure as recited.

-192-

29. The process according to claim 28
wherein R¹ is a single-ringed cyclohydrocarbyl,
heterocyclo, aryl or heteroaryl substituent that is
5- or 6-membered, and is itself substituted at its
5 own 4-position when a 6-membered ring and at its own
3- or 4-position when a 5-membered ring with a
substituent R⁴ selected from the group consisting of
one other single-ringed aryl or heteroaryl group, a
C₃-C₁₄ hydrocarbyl group, a C₂-C₁₄ hydrocarbyloxy
10 group, a phenoxy group, a thiophenoxy group, an
anilino group, a 4-thiopyridyl group, a phenylazo
group, a phenylureido group, a nicotinamido group, an
isonicotinamido group, a picolinamido group and a
benzamido group.

15

30. The process according to claim 28
wherein said R¹ substituent is PhR⁴ in which Ph is
phenyl substituted with R⁴ at the 4-position, and R⁴
is a phenyl, phenoxy, anilino, thiophenoxy,
20 phenylazo, benzamido, nicotinamido, isonicotinamido,
picolinamido or phenylureido group

31. The process according to claim 28
wherein said R¹ substituent is PhR⁴ in which Ph is
25 phenyl substituted with R⁴ at the 4-position, and
said R⁴ is a phenyl, phenoxy, anilino, thiophenoxy,
phenylazo, benzamido, nicotinamido, isonicotinamido,
picolinamido or phenylureido group that is
substituted at the meta- or para-position or both
30 with a moiety that is selected from the group
consisting of a halogen, a C₁-C₉ hydrocarbyloxy
group, a C₁-C₁₀ hydrocarbyl group, a di- C₁-C₉

-193-

hydrocarbylamino group, a carboxyl C₁-C₈ hydrocarbyl group, a C₁-C₄ hydrocarbyloxy carbonyl C₁-C₄ hydrocarbyl group, a C₁-C₄ hydrocarbyloxy carbonyl C₁-C₄ hydrocarbyl group and a carboxamido C₁-C₈ hydrocarbyl group, or is substituted at the meta- and para-positions by two methyl groups or by a methylenedioxy group.

32. The process according to claim 28
10 wherein said R¹ substituent has a length greater than that of an octyl group and less than that of a stearyl group.

33. The process according to claim 28
15 wherein said R⁴ is a phenoxy or thiophenoxy group that is unsubstituted.

34. The process according to claim 28
wherein said compound is administered a plurality of
20 times.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/04297

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/607; 546/193, 194, 189; 544/122, 130; 514/063, 212, 235.5, 256, 326, 318, 326

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	EP 0,780,386 A (HOFFMANN-LA ROCHE AG) 25 June 1997, entire document.	1-34

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* "A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* "E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
* "O" document referring to an oral disclosure, use, exhibition or other means		
* "P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 13 APRIL 1998	Date of mailing of the international search report 10 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MATTHEW V. GRUMBLING Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/04297

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

C07D 309/08, 211/54, 213/64, 401/06, 407/12, 413/12, 405/12, A61K 31/35, 31/445

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

540/607; 546/193, 194, 189; 544/122, 130; 514/063, 212, 235.5, 256, 326, 318, 326

THIS PAGE BLANK ~~EXPTO~~